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Towards continued and affordable accessibility of innovative drugs: sustainable development and efficient use of medicines

Edited by
Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani, Rob ter Heine, Atse Huisman, Denise Van Den Berg, Bettina Ryll, Maria Judit Molnar and Saco De Visser

Published in
Frontiers in Pharmacology
Frontiers in Immunology

ISSN 1664-8714
ISBN 978-2-8325-5707-5
DOI 10.3389/978-2-8325-5707-5

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Towards continued and affordable accessibility of innovative drugs: sustainable development and efficient use of medicines

Topic editors

Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani — CZ Health Insurance, Netherlands

Rob ter Heine — Radboud University Medical Centre, Netherlands

Atse Huisman — Health Insurers Netherlands, Netherlands

Denise Van Den Berg — Treatmeds Foundation, Netherlands

Bettina Ryll — Melanoma Patient Network Europe, Sweden

Maria Judit Molnar — Semmelweis University, Hungary

Saco De Visser — Centre for Future Affordable and Sustainable Therapy development (FAST), The Hague, Netherlands

Citation

Barjesteh Van Waalwijk Van Doorn-Khosrovani, S., ter Heine, R., Huisman, A., Van Den Berg, D., Ryll, B., Molnar, M. J., De Visser, S., eds. (2024). *Towards continued and affordable accessibility of innovative drugs: sustainable development and efficient use of medicines*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5707-5

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frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 05 November 2024
DOI 10.3389/fphar.2024.1490853

OPEN ACCESS

EDITED AND REVIEWED BY
Bernd Rosenkranz,
Fundisa African Academy of Medicines Development, South Africa

*CORRESPONDENCE
Sahar Barjesteh van Waalwijk van Doorn-Khosrovani,
sahar.van.waalwijk@cz.nl

RECEIVED 03 September 2024
ACCEPTED 21 October 2024
PUBLISHED 05 November 2024

CITATION
Huisman AH, van den Berg D, de Visser S, Ryll B and Barjesteh van Waalwijk van Doorn-Khosrovani S (2024) Editorial: Towards continued and affordable accessibility of innovative drugs: sustainable development and efficient use of medicines.
Front. Pharmacol. 15:1490853.
doi: 10.3389/fphar.2024.1490853

Editorial: Towards continued and affordable accessibility of innovative drugs: sustainable development and efficient use of medicines

Atse H. Huisman[1,2], Denise van den Berg[3], Saco de Visser[4], Bettina Ryll[5,6] and Sahar Barjesteh van Waalwijk van Doorn-Khosrovani[1,7]*

[1]Department of Medical Oncology, Leiden University Medical Centre, Leiden, Netherlands, [2]Department of Health Policy, Health Insurers Netherlands, Zeist, Netherlands, [3]Treatmeds Foundation, 's-Hertogenbosch, Netherlands, [4]Centre for Future Affordable and Sustainable Therapy Development (FAST), The Hague, Netherlands, [5]Melanoma Patient Network Europe, Uppsala, Sweden, [6]Stockholm School of Economics Institute for Research, Stockholm, Sweden, [7]Medical Department, CZ Health Insurance, Tilburg, Netherlands

KEYWORDS

affordability and accessibility of medicines, expensive drugs, access, compounding, de-escalation, cost-efectiveness, repurposing, precision medicine

Editorial on the Research Topic
Towards continued and affordable accessibility of innovative drugs: sustainable development and efficient use of medicines

The rising cost of medicines burdens healthcare systems and limits access to novel therapies worldwide. Therefore, sustainable solutions to enhance access and foster innovation are crucial. To highlight current strategies and exchange ideas, we created a Research Topic titled "Towards continued and affordable accessibility of innovative drugs: sustainable development and efficient use of medicines." Our primary goal was to provide practical recommendations and insights to support healthcare systems. Here we discuss the key topics covered in the Research Topic.

1 Addressing uncertainty regarding clinical value

Health Technology Assessment (HTA) bodies and healthcare funders often evaluate the clinical value of new drugs before reimbursement. Several factors can contribute to uncertainty regarding the clinical value; e.g., the validity of surrogate endpoints, concerns about generalisability and lack of long-term efficacy data. In our Research Topic, (Vallano et al.) emphasize the importance of evaluating clinically relevant variables (i.e., overall survival and quality of life) over surrogate endpoints. Broader eligibility criteria can improve the real-world representativeness of clinical studies.

Fagereng et al. studied the impact of these uncertainties on reimbursement decisions in Norway. Drugs with higher certainty of relative effectiveness were more likely to be

reimbursed, and at higher costs, than those with lower certainty. This underscores the importance of robust relative-effectiveness data for guiding policy and resource allocation.

In the Netherlands, rising healthcare costs have resulted in a halt in automatic reimbursement for new drugs with a high budget impact used in hospitals. Since 2015, a so-called 'Coverage Lock' has been implemented by the government to assess these drugs and establish financial arrangements with the manufacturers. Bomhof et al. explored the ethical aspects of reduced drug access under this policy. Although most stakeholders interviewed favoured access through free-of-charge programmes by manufacturers during the Coverage Lock, they expressed concerns about the lack of transparency and unequal access. Creating a national platform such as the Dutch Drug-Access Protocol (Zeverijn et al., 2022), that provides equal access, gathers real-world data, and incorporates a pragmatic, outcome-based risk-sharing model, as well as finding common ground with pharmaceutical companies (Dane et al.), may offer a solution.

Another common challenge discussed in our Research Topic was access to Advanced Therapy Medicinal Products (ATMPs). Rejon-Parrilla et al. identified barriers, such as high initial costs and insufficient long-term effectiveness data, which can burden healthcare systems. With the new HTA regulation starting in 2025, anticancer drugs and ATMPs will undergo joint clinical assessments. This could enable collaborative evidence generation and potentially improve access in the future.

2 Increase treatment (cost) effectiveness by preventing overtreatment and de-escalation strategies

With the launch of every new therapy, treatment optimisation studies are essential for refining drug use, improving patient outcomes, and, when possible, enhancing cost-effectiveness. Subjecting patients to unnecessary long treatment duration or high doses of medicine exposes them to avoidable side effects, which can negatively impact their quality of life. Furthermore, overtreatment strains the environment and healthcare resources, including time, personnel and facilities. Pharmaceutical companies themselves usually lack incentives to address overtreatment or explore alternative dosing regimens, as this can slow down or jeopardise developmental or business outcomes. Once the drug is commercially available, a personalised approach (Walia and Prasad) and exploring de-escalation strategies (Buma et al.; van Riel et al.; Dane et al.) are in the interest of both patients, payers, healthcare professionals and society. In our Research Topic, Walia and Prasad challenge the use of an indefinite anticoagulation strategy for patients with unprovoked venous thromboembolism and Buma et al. explore de-escalation regimens of immune-checkpoint inhibitors in lung cancer, alongside extensive biomarker research to address overtreatment (van Riel et al.). The latter is funded by a national fund (Treatmeds Foundation) (Barjesteh van Waalwijk van Doorn-Khosrovani et al., 2022) that specifically supports cost-efficiency studies (van Riel et al.). However, in an ideal setting, dose minimisation strategies should already be part of the initial drug development process.

3 Reducing waste

Reducing waste of medicines preserves valuable resources and minimises environmental impact. Dane et al. propose that same day scheduling of patients for the same treatment reduces waste, as prepared IV therapy for a no-show can be given to another patient. For the medicines administered by patients at home, which may have a high chance of being left unused (for instance, due to side effects, disease progression, or death), hospital pharmacies can deliver supply every 2 weeks or monthly to prevent spillage, though the environmental impact of more frequent deliveries should be carefully considered as part of a holistic strategy. Also collecting and re-dispensing unused oral anticancer drugs can reduce waste and save money (Dane et al.; Smale et al., 2023). However, to make this possible as part of routine care, local and regional regulatory guidance needs to be developed to determine the circumstances under which medicine re-dispensing is acceptable. In the absence of such guidance, oncologists should aim to prescribe just enough medication for patients to use at home, minimising the risk of wasting unused surplus when therapy changes are necessary (Dane et al.) while being mindful not to increase the burden of care for patients.

4 Combination therapies and challenges regarding their (cost) effectiveness

Assessment of a single technology is relatively straightforward, involving analysis of costs and outcomes for a particular intervention. However, assessing combination therapies or multiple technologies (several examples were submitted to our Research Topic) (Huang et al.; He et al.) is more complex. This complexity arises, for instance, from uncertainties regarding drug synergy, the cumulative financial burden and complex negotiations with various companies. Consequently, cost-effectiveness analysis of some new combination therapies show unfavourable high cost per QALY, even for high-income countries (Xiang et al.; Huang et al.).

In multiple myeloma, for instance, the current paradigm involves upfront triplet or quadruplet regimens, which can result in high toxicity and costs. It is unknown whether sequential use of these agents can lead to similar or even superior overall survival and quality of life. Walia et al. advocate for more trial data justifying the use of such multi-drug regimens.

In our Research Topic, He et al. discuss the challenges of economic analyses of combined technologies in first-line treatment for advanced hepatocellular carcinoma in China, where economic development varies significantly among provinces. Also, in the EU, diverse economic conditions and healthcare systems lead to varying cost-effectiveness thresholds among members, resulting in disparities in healthcare access.

Academic hospitals (Dane et al.) and cooperative study groups (Walia et al.) are well-suited to champion research agendas focused on studying the sequential use of therapies rather than combinations for relevant therapy classes, thereby reducing the burden of toxicity and contributing to the sustainability and affordability of healthcare systems.

5 In-house development and production

Academic hospitals often possess specialised expertise and the agility to develop and/or produce medicines in response to unmet medical needs. For instance, several ATMPs in use today had their initial prototypes developed in academic hospitals (Dane et al.). A recent EMA (European Medicines Agency) pilot aims to help academics further develop ATMPs. Netherlands currently reimburses an in-house adoptive cell therapy with tumour-infiltrating lymphocytes (TILs) (Rohaan et al., 2022) for advanced melanoma and two non-profit radiopharmaceuticals, prepared by hospitals (Dane et al.).

Compounding pharmacies can play a crucial role in producing medicines that are scarce or have been discontinued by pharmaceutical companies, ensuring ongoing access for patients. In some cases, compounded medicine can also serve as a cost-effective alternative to the commercial counterpart (Dane et al.; Bouwhuis et al.). Overall, academia-driven drug development could be instrumental in guiding novel public-private partnerships towards more affordable therapies.

6 Repurposing precision medicine in oncology

Drug repurposing uses approved medicines for new indications, offering alternative treatments or addressing unmet medical needs. This approach significantly lowers R&D costs, since these drugs have already passed safety assessments and demonstrated clinical efficacy. In the Netherlands, the Drug Rediscovery Protocol (DRUP) (van der Velden et al., 2019; van Waalwijk van Doorn-Khosrovani et al., 2019) an adaptive platform trial, provides off-label access to targeted therapies and immune-checkpoint inhibitors based on molecular tumour profiles. It offers treatment to patients who have exhausted standard-of-care options and generates necessary evidence for reimbursement. Currently, eighteen European countries collaborate in the PRIME-ROSE consortium (Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials) (Taskén et al., 2024) to create a collaborative DRUP-like platform and accelerate drug development for rare indications. Also other EU funded platforms REMEDI4ALL and REPO4EU aim to boost drug repurposing.

Nevertheless, relying solely on public funding for drug repurposing trials may be unrealistic. Creating a clear path to drug registration and developing transparent, cost-based-plus pricing models that appeal to private investors can further stimulate drug repurposing. In the Netherlands, the centre for Future Affordable and Sustainable Therapy development (FAST) (de Visser et al., 2024) explores this area to better align innovation and affordability in drug development.

7 Conclusion

In this Research Topic, 'Towards continued and affordable accessibility of innovative drugs: Sustainable development and efficient use of medicines', we present a snapshot of ideas, insights, and ongoing efforts aimed at ensuring the continued and affordable accessibility of innovative drugs, as well as promoting sustainable development and the efficient use of medicines. It is important to realise that there is often a substantial knowledge gap after the launch of new drugs. This gap should be systematically and independently addressed to optimise treatment regimens. A recent European initiative is the Cancer Medicines Forum (CMF) (Saesen et al., 2022), a platform established to identify treatment optimisation questions and priorities, and help to address evidence gaps. National and regional funds supporting such initiatives can play a crucial role in improving cost-efficiency and reducing overtreatment.

Author contributions

AH: Writing–review and editing, Writing–original draft. DV: Writing–review and editing, Writing–original draft, Supervision. SD: Writing–review and editing. BR: Writing–review and editing. SB: Writing–review and editing, Writing–original draft, Supervision, Conceptualization.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Part of the editorial work for this Research Topic is funded by the European Union under the Horizon Europe programme: The Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trial (PRIME-ROSE) (grant: 101104269).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Author disclaimer

Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

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frontiers | Frontiers in Pharmacology

TYPE Opinion
PUBLISHED 03 July 2023
DOI 10.3389/fphar.2023.1231720

OPEN ACCESS

EDITED BY
Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani,
CZ Health Insurance, Netherlands

REVIEWED BY
Hans Westgeest,
Amphia Ziekenhuis, Netherlands
Matthijs Versteegh,
National HealthCare Institute (ZIN), Netherlands
Edwin Van Breugel,
Independent researcher, Eindhoven, Netherlands

*CORRESPONDENCE
Vinay Prasad,
vinayak.prasad@ucsf.edu

RECEIVED 30 May 2023
ACCEPTED 16 June 2023
PUBLISHED 03 July 2023

CITATION
Walia A, Haslam A, Tuia J and Prasad V (2023), Multiple myeloma: challenges with deciding the optimal sequencing strategy.
Front. Pharmacol. 14:1231720.
doi: 10.3389/fphar.2023.1231720

Multiple myeloma: challenges with deciding the optimal sequencing strategy

Anushka Walia[1], Alyson Haslam[2], Jordan Tuia[2] and Vinay Prasad[2]*

[1]School of Medicine, University of California, San Francisco, San Francisco, CA, United States, [2]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, United States

KEYWORDS

multiple myeloma, combination therapy, triplet regimen, doublet regimen, sequencing strategy

Commentary

The therapeutic landscape for multiple myeloma (MM) has witnessed great advances over the past two decades, with more than 20 FDA-approved drugs currently available. The latest NCCN (Version 3.2023) guidelines recommend at least a triplet regimen as induction therapy for patients with newly diagnosed MM and adequate performance status. Quadruplet regimens are expected to be front-line in the near future, with trials evaluating combinations of daratumumab and bortezomib-lenalidomide-dexamethasone (VRd) currently underway. Yet despite the abundance of drug options for MM, the optimal sequencing strategy of these agents has not been determined. In this commentary, we contend that triplet and quadruplet combination therapies have not proven superiority over sequential therapy that starts with fewer upfront agents and reserves additional drugs for progression. Instead, randomized trials which have failed to adequately document or which have given suboptimal treatment at progression form the basis of the current dogma.

PFS may not be a valid endpoint in studies evaluating combination over sequential therapy

Overall survival (OS) and health related quality of life (QoL) are the two important patient-centered endpoints in oncology. Historically in oncology, improvements in surrogates such as progression-free survival (PFS) or response rate have not been sufficient to prove superiority of combination over sequential therapy, when these benefits do not translate to improved OS or QoL. For instance, a 2003 phase III clinical trial comparing the combination of doxorubicin and paclitaxel vs. single agent doxorubicin or paclitaxel for metastatic breast cancer showed that combination therapy yielded superior overall response rates and longer time to treatment failure. (Sledge et al., 2003) Despite these benefits, the study authors rejected combination therapy on the basis of its failure to improve OS or QoL. Instead, the authors preferred single agent sequential therapy. The same logic has not been applied to multiple myeloma.

Multiple pivotal phase 3 clinical trials evaluating combination vs sequential therapy use primary endpoints of PFS. This raises several concerns. First, the validity of PFS as a surrogate for OS is questionable. In a recent analysis of 21 RCTs on newly diagnosed MM, the correlation (R^2) between PFS and OS was found to be just 0.65, which is "weak" according to standards published by the independent German Institute for Quality and Efficiency in Healthcare and suggests that improvements in PFS may not predict OS benefit. (Cliff and Rehman Mohyuddin, 2022; Etekal et al., 2023) While some MM RCTs such as SWOG

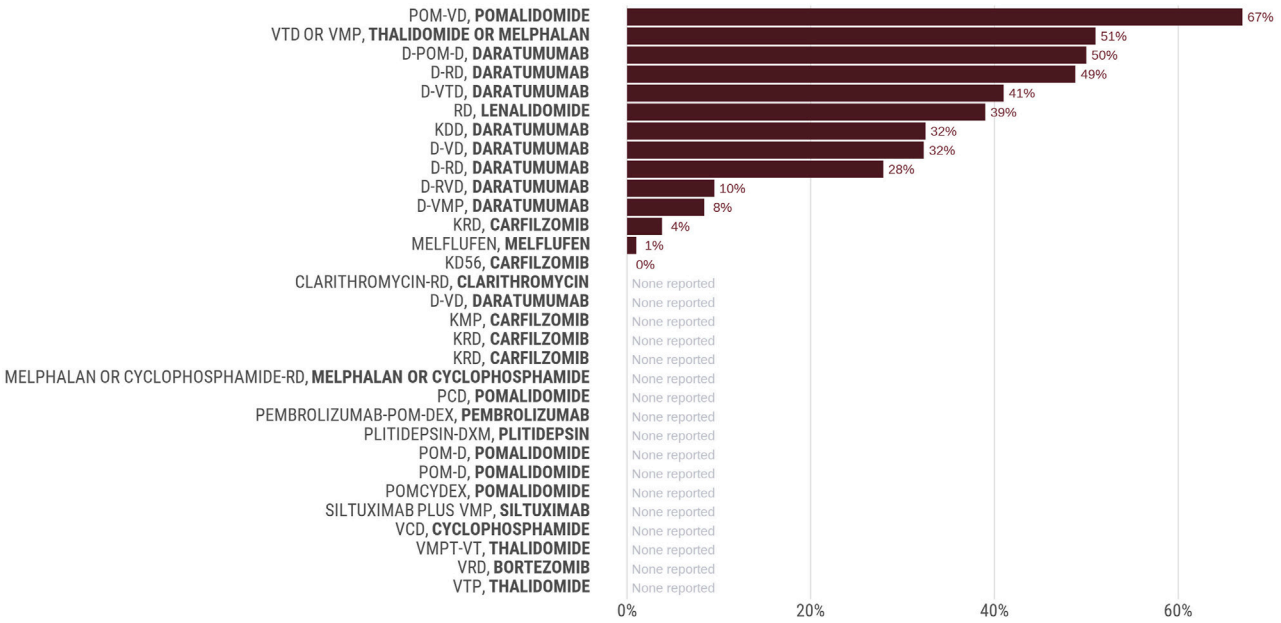

FIGURE 1
Percentage of patients who received experimental drug in a subsequent line.

0777 and MAIA showed PFS and OS benefits with addition of bortezomib or daratumumab, respectively, to Rd at subsequent follow up, this was not the case in other trials. OCEAN and BELLINI demonstrated worse OS in experimental arms despite initial PFS gains (Cliff and Rehman Mohyuddin, 2022). The use of PFS as a primary endpoint is further complicated by the fact that progression has both clinical and biochemical definitions, which vary in prognostic value and are rarely reported separately in clinical trials (Villaruz and Socinski, 2013).

Second, even if PFS is a useful endpoint when establishing clinical benefit of a drug, this does not mean that it is equally valid to move a drug that has already proven PFS benefit up a treatment regimen. (Rajkumar et al., 2011). In trials evaluating triplet vs doublet therapy, patients in the doublet arm may receive the third drug at progression. A PFS benefit in the triplet arm is expected because each drug in the regimen has proven efficacy. Since patients may be able to achieve the same benefit by taking the third drug at a later time, the combination may not be superior to sequential therapy.

Interpretation of OS benefit is confounded by lack of transparent reporting of post-protocol therapies

Transparent reporting of post-protocol therapies in randomized controlled trials (RCTs) is essential to compare the efficacies of combination and sequential therapies. Yet, one systematic review found that only 43.7% of 103 MM RCTs reported post-protocol therapies. (Mohyuddin et al., 2021a). Notably, the SWOG 0777 study, which established VRd over Rd as the standard of care in newly diagnosed MM, did not capture post-protocol therapies. According to the most recent follow-up, it is still unclear how many patients in SWOG 0777's Rd arm received bortezomib at progression. Although the trial enrolled in the USA, where bortezomib was available, explicit knowledge of this information is key to ascertain the superiority of VRd over Rd with bortezomib made available as a salvage agent.

Figure 1 reports the rates at which control groups received the experimental drug in a subsequent line in 32 RCTs evaluating combinations including daratumumab or carfilzomib, two drugs initially authorized by the FDA authorization in the salvage setting. Among 14 trials that reported subsequent therapies, the average rate was 29%, with numbers varying between 0% and 67%. In the MAIA study comparing daratumumab-Rd vs. Rd, 49% of patients in the Rd arm received daratumumab in a latter line. None of the three most common regimens received by control arm patients at progression (bortezomib; bortezomib-cyclophosphamide-dexamethasone, bortezomib-melphalan-prednisone) included daratumumab (Mohyuddin et al., 2021a). Rates were even lower in the ALCYONE study evaluating the addition of daratumumab to bortezomib-melphalan-prednisone (VMP), in which only 8.4% of patients in the VMP arm received a daratumumab-containing regimen as first line subsequent therapy. The PFS and OS improvements seen in experimental arms of such studies may not have existed if more patients in the control arm received the proper drug at progression. Thus, the question of whether combination therapy is superior to sequential remains unassessed. Trials have tested a trivial question of

whether receiving the drug at some point during the cancer journey is better than never receiving it at all, but the question facing patients and doctors is when to give the drug to optimize outcomes.

Further complicating the interpretation of RCTs comparing MM regimens is the fact that control groups do not always reflect the current standard of care. In these studies, it is not possible to determine whether response rates reflect the superiority of the experimental treatment or the inferiority of the control treatment. A significant number of phase 3 MM RCTs have substandard control arms despite a superior regimen existing before or during the trial (Mohyuddin et al., 2021b). The MAIA, KEYNOTE-185 (pembrolizumab-Rd vs. Rd), and TOURMALINE-MM2 (ixazomib-Rd vs. Rd) trials for newly diagnosed MM illustrate a tension. Each of these trials had Rd control arms, despite results from SWOG 0777 emerging during enrollment. If the authors had accepted the superiority of VRd over Rd, which most likely did, then they were enrolling patients onto inferior control groups.

Trial findings may not be generalizable to real world

Multiple myeloma has a median age of diagnosis of 70 years with a third of patients over 75. A significant proportion of MM patients are frail and have multiple comorbidities, both predictors of worse treatment outcomes. The benefits that triplet therapy shows in clinical trials may not translate to the real world, given that several combination therapies carry significant toxicities and trial criteria select patients with better performance status and fewer comorbidities.

Medhekar et al., 2022 evaluated outcomes among newly diagnosed non-transplanted MM patients treated with first line VRd in a real-world setting (Medhekar et al., 2022). They found median PFS to be 26.5 months, substantially lower than the 43 months reported in SWOG S0777's VRd arm. Real world patients were also older (64% of patients over 65% vs. 38%) and more frail (48% vs. 21%) than those enrolled in the clinical trial.

The advantage of triplet over doublet therapy is less evident in the community setting. The community-based Phase IIIB UPFRONT trial compared bortezomib-dexamethasone (VD) with bortezomib-thalidomide-dexamethasone (VTD) and bortezomib-melphalan-prednisone (VMP) as induction therapy for newly diagnosed transplant ineligible MM. No differences in PFS between VD, VTD, and VMP were found, partly due to greater rates of adverse events and treatment discontinuation associated with triplet therapy.

Some real-world data suggests that initial doublet therapy with subsequent addition of a third drug if necessary can lead to successful outcomes. One retrospective study examined newly-diagnosed non-transplanted MM patients who received initial therapy with Rd and switched to a triplet therapy if VGPR was not achieved (Takezako et al., 2019). From VGPR rates of 32.3% after Rd alone and 69% after non-responders received an additional drug, the authors concluded that Rd is sufficient as initial therapy.

Recommendations

When it comes to multiple myeloma, our overarching concern is that current paradigms will lead to more drugs given upfront to more patients, with greater attendant toxicity and cost, while patients and doctors remain fundamentally unsure if similar or superior overall survival and QOL could be achieved from careful, sequential use of these agents. Researchers have potential to ameliorate this situation.

First, transparent reporting of post-protocol therapies should be the standard in clinical trials comparing multidrug regimens and must be mandated by regulatory agencies. The majority of MM RCTs do not report this data and among those that do, the frequency of inadequate post-protocol care received by the control arm is alarming. Patients in control arms should have access to the experimental drug at minimum, if it has been authorized in the U.S. in a subsequent line.

Second, the use of PFS as a primary endpoint in trials investigating the addition of a drug to an existing therapeutic regimen should be avoided. A PFS benefit of a combination regimen is meaningless if the same OS or QoL can be achieved by providing the experimental drug in subsequent lines. While collecting OS data may require longer follow-up, this is not the case in all disease settings such as relapsed/refractory MM. For instance, for double refractory patients, median OS is 9 months, while the median PFS is 5 months—just a 4 months difference (Lee et al., 2013). Yet, the BELLINI and OCEAN trials used primary endpoints of PFS. If earlier results are desired, another possible option proposed by Cliff et al. is the intermediate endpoint, "PFS2," which is equal to time until disease progression or death during the trial and after the first post-protocol therapy (Cliff and Rehman Mohyuddin, 2022). This can enable comparison between sequential and combination approaches until final OS results are achieved.

Third, QoL should be measured in all RCTs assessing combination therapies. QoL data has been absent from several practice-changing RCTs including SWOG 0777 (in which collecting QoL data is more important given bortezomib's association with peripheral neuropathy). QoL measurements should be recorded throughout the length of the patient's cancer journey, including throughout treatment and beyond progression (Haslam et al., 2020). Moreover, financial toxicity of multi-drug therapy should be accounted for in QoL scores and may be less apparent in the trial setting (Olivier et al., 2023).

Fourth, additional studies are necessary to determine how clinical trial findings translate to the real world, where significant differences in health status, financial burden, and treatment toxicity may exist. While some studies have highlighted discrepancies between real-world and trial outcomes in MM, they are limited by sample size and data on real-world treatment outcomes is currently sparse (Bertamini et al., 2022). Elsewhere, we have proposed the use of registry based pragmatic trials to achieve this aim, though other strategies may be complementary (Banerjee and Prasad, 2021).

Lastly, additional funding is required to perform trials specifically comparing "all at once" and sequential approaches to MM therapy. Existing RCTs were not designed for this purpose, given that they were funded by pharmaceutical companies and funding sources outside of industry are unfortunately limited. Lack of reporting of post-protocol care has further precluded any comparison of treatment strategies. Cooperative groups are well suited to champion this research agenda. Until we have this data, combination regimens with

careful consideration of individual risk factors, treatment side effects, cost, and patient preferences can guide therapy in MM.

Conclusion

Outcomes in MM have vastly improved in recent years as a result of novel anticancer agents and multidrug regimens. Despite the popularity of triplet induction therapy and a push towards quadruplets for MM, uncertainty remains. One treatment approach favors aggressive therapy with multi-drug combination regimens, the goal being to maximize initial response rates. A second approach favors sequential therapy that starts with fewer, less toxic agents and reserves a greater number of options for salvage lines.

Most clinical studies have shown that triplet or quadruplet regimens lead to deeper initial response rates than doublet therapy. However, it is not clear whether frontline doublet therapy followed by additional treatment upon progression would yield any less benefit. This question cannot be answered based on current trial data due to lack of reporting of post-protocol therapies or substandard post-protocol care. The survival and quality of life benefits of combination therapy are unclear for similar reasons. We do know that combination therapy leads to greater adverse effects, especially in older, frail patients that are typically excluded from clinical trials. Further data is necessary to justify the use of costly, toxic multi-drug regimens over sequential therapy that may prove just as favorable.

Author contributions

AW: original draft preparation; AH: data collection; JT: data presentation; VP: conceptualization, reviewing, and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

VP's Disclosures: (Research funding) Arnold Ventures (Royalties) Johns Hopkins Press, Medscape, and MedPage (Honoraria) Grand Rounds/lectures from universities, medical centers, non-profits, and professional societies. (Consulting) United Healthcare and OptumRX. (Other) Plenary Session podcast has Patreon backers, YouTube, and Substack.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1231720/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Perspective
PUBLISHED 28 August 2023
DOI 10.3389/fphar.2023.1264951

OPEN ACCESS

EDITED BY
Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani,
CZ Health Insurance, Netherlands

REVIEWED BY
Silvia Van Der Flier,
VGZ, Netherlands
Denise Van Den Berg,
Treatmeds Foundation, Netherlands
Berna C. Özdemir,
Bern University Hospital, Switzerland

*CORRESPONDENCE
Aniek Dane,
a.dane@erasmusmc.nl

RECEIVED 21 July 2023
ACCEPTED 16 August 2023
PUBLISHED 28 August 2023

CITATION
Dane A, van Leeuwen R, Hoedemakers M, van der Kuy H and Sleijfer S (2023), Combatting the rising costs of cancer drugs; interventions from a university hospital's perspective.
Front. Pharmacol. 14:1264951.
doi: 10.3389/fphar.2023.1264951

Combatting the rising costs of cancer drugs; interventions from a university hospital's perspective

Aniek Dane[1]*, Roelof van Leeuwen[1], Maaike Hoedemakers[2], Hugo van der Kuy[1] and Stefan Sleijfer[3]

[1]Department of Hospital Pharmacy, Erasmus MC, Rotterdam, Netherlands, [2]Department of Market Strategy and Healthcare Financing, Erasmus MC, Rotterdam, Netherlands, [3]Executive Board, Erasmus MC, Rotterdam, Netherlands

Rapid increase in cost continues to have negative impact on patients' accessibility to life-changing anticancer medications. Moreover, the rising cost does not equate to similar increase in medication effectiveness. We recognise our responsibility as a university hospital to tackle this imbalance and strive to provide high quality, sustainable, affordable and accessible care. An active approach in cost containment of expensive and innovative cancer drugs was adopted in our organisation to safeguard accessibility and improve quality of life for patients. In this article, we described four inverventions: 1) identify right patient and minimise overtreatment, 2) in-house medicine production for selected indications, 3) minimise medicine spillages and 4) effective procurement strategies. We call on other hospitals to take action and, favourably, to collaborate on a European level. Together, we will safeguard the current and future care of our patients.

KEYWORDS

cancer drugs, drug life cycle, university hospital, precision dosing, biomarkers, efficiency, sustainable healthcare, self-manufacturing

1 Introduction

We live in prosperous times when it comes to cancer care (Sleijfer and Verweij, 2016). Thanks to the advance of science and technology patients have better outcomes and quality of life following their diagnosis, even for rare indications.

According to the Dutch national figures of the last 30 years, 10-year survival rates have increased from 43% (1991–2000 period) to 59% (2011–2020 period)[1]. Meanwhile, cancer incidence increased from 58,505 patients in 1991 to 124,109* in 2022 (*preliminary figures)[2] which is at a slower pace compared to the increasing costs of cancer drugs (Hofmarcher et al., 2020). The expenditure on reimbursed expensive medications in hospitals has increased

1 https://applicatie.nkrcijfers.nl/?fs%7Cepidemiologie_id=527&fs%7Ctumor_id=1&fs%7Coverlevingssoort_id=532&fs%7Cperiode_van_diagnose_id=601%2C600%2C599%2C598%2C597%2C596&fs%7Cjaren_na_diagnose_id=688%2C689%2C690%2C691%2C692%2C693%2C694%2C695%2C696%2C697%2C698%2C699&cs%7Ctype=line&cs%7CxAxis=jaren_na_diagnose_id&cs%7Cseries=periode_van_diagnose_id&ts%7CrowDimensions=periode_van_diagnose_id&ts%7CcolumnDimensions=jaren_na_diagnose_id&lang%7Clanguage=nl.

2 https://nkr-cijfers.iknl.nl/#/viewer/9cdbca8b-084c-4ab9-8ed5-12f719441877.

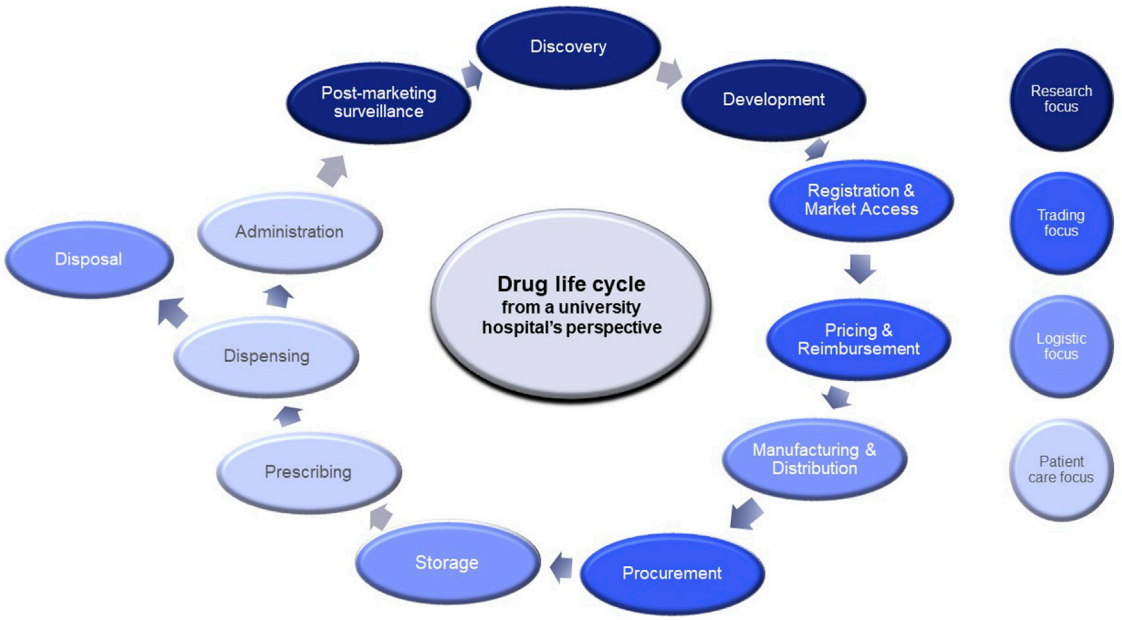

FIGURE 1
Drug life cycle from a university hospital's perspective.

from €1.24 billion in 2012 to €2.64 billion in 2021, with 50% of this amount being attributed to cancer treatments[3] (SiRM, 2022).

As a result of improved outcomes, better diagnostics, increasing incidence and more and expensive treatment options, total spending on cancer care is rising posing a potential threat to the accessibility of these drugs (Brouwer et al., 2019; NZa, 2022).

Pharmaceutical companies justify the higher prices with reasons such as the costs of research & development (R&D) (Prasad and Mailankody, 2017; DiMasi and Pieters, 2018) and creating value for patients and society (Prasad et al., 2017; Picozzi et al., 2020). However, clinical benefit and costs of cancer treatment are not directly associated (Vokinger et al., 2020).

Currently, with advanced medicinal therapeutic products (ATMPs) such as gene and cell therapies entering the market at soaring prices, new pricing models need to be developed to safeguard patient access and prevent unjustified public funding. To accelerate patient access to innovative medicines and to manage the increase in drug expenditure, governments, policy makers, reimbursement agencies and health insurers, often in collaboration with the pharmaceutical industry, have developed several tools such as managed entry agreements, external reference pricing, Health Technology Assessment (HTA), and (international) horizon scanning of new drugs and extensions of indications coming to market. As stated in the Pharmaceutical Strategy for Europe of the European Commission, solutions along the entire drug life cycle should be considered as it offers a more comprehensive and integrated approach to address the challenge of rising drug expenditure. Furthermore, all stakeholders should be involved in tackling this problem (European Commission, 2020). In addition to current efforts, university hospitals should be more aware of the rising drug costs and be pro-active in taking matter in their hands.

2 University hospital's social responsibility: vision of Erasmus MC

As one of the largest university hospitals in the Netherlands, we aim to contribute to a sustainable, affordable and accessible healthcare system. We have a responsibility to curb expenditure growth and ensure timely access to drugs for patients, while continue to improve patient care and quality of life. As university hospital, we are involved throughout the drug life cycle through healthcare delivery, education and academic research (see Figure 1).

Our involvement starts with conducting (bio) medical research leading to new anticancer drugs, then performing or coordinating clinical trials and collect real-world data for, e.g., post-marketing surveillance. In clinical settings, clinicians prescribe anticancer therapies while hospital pharmacy provides the medications or in some cases, manufactures them. Furthermore, we are involved in negotiating drug prices and discounts upon procurement. Here we described how our organisation delivers sustainable and affordable cancer care through several practical interventions.

2.1 Targeting the right patients

Before market entry of a new systemic anticancer therapy, the therapy must be rigorously assessed in a clinical trial, ideally with randomisation. Approval will be granted after the new therapy has

3 https://www.vektis.nl/intelligence/publicaties/factsheet-dure-geneesmiddelen.

demonstrated its benefits, preferably when the overall benefits, e.g., prolonging survival and/or improving quality of life outweigh the risks of toxicity and adverse drug reactions. To guide decisions on the value of novel treatments, criteria such as in the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) (Cherny et al., 2017) have been developed which describes what magnitude of effect should be anticipated in the curative and non-curative setting.

In many clinical trials, participants are usually included based on stringent eligibility criteria such as tumour type, tumour stage, clinical performance, organ function, co-morbidity, presence of brain metastases, and prior treatments. These strict criteria unfortunately do not reflect the wider population. In clinical practice, criteria used to decide if a patient should receive a particular treatment are more lenient. An analysis in the Netherlands (van Zeijl et al., 2020) found that 40% of 2,536 systemically treated patients with advanced melanoma failed to meet the eligibility criteria used in the clinical trial. Quite often, patients included in clinical trials have better prognosis than the target population. For example, a study has reported that the median overall survivals between eligible and ineligible patients are 23 and 8.8 months respectively.

(van Zeijl et al., 2020). In many other tumour types and treatment regimens the same holds true. Worse outcomes in real-life populations are observed compared to the outcomes seen in the clinical trials due to less stringent selection of patients (Di Maio et al., 2019). Consequently, the benefit-risk ratio, which was deemed acceptable for patients accrued in the registration study, will not be met in the real-life populations. Therefore, many patients are exposed to toxicity from treatments that may not be outweighed by the benefits of the treatment. Likewise, expenditure to achieve the promised result is higher than reported during appraisal of the new therapy. In avoidance, treatments should be given only to patients who fulfil the same eligibility criteria of the clinical trial for that particular drug. Obviously, this is frequently not the case in practice. This underlines the necessity of aligning the eligibility criteria in clinical trials. By doing so, data collected in clinical trials will be applicable to a wider population which, successively, will reduce the risk of exposing patients to toxicity unnecessarily.

2.2 Clinical studies to reduce treatment burden for patients and to minimise costs of overtreatment

Overdiagnostics and overtreatment of cancer patients are very common and, though maybe inherent to cancer care, should be prevented where possible (Esserman and Thompson, 2013; Katz et al., 2018). The consequences of overtreatment are serious such as unnecessarily exposing patients to treatment toxicity and financial loss associated with overtreatment including medication administration, and adverse event management cost. There are several forms of overtreatment.

Many cancer patients display intrinsic resistance to treatment or develop resistance during treatment. It is important to detect failure to therapy as quickly as possible by scientific research and to swiftly implement effective therapies into daily clinical practice. Patients with intrinsic or primary resistant disease to a certain therapy can be identified by using predictive biomarkers. A great example is the identification of mutations in KRAS, NRAS, and BRAF as predictive markers in patients with metastatic colorectal cancer (mCRC) who are candidates for monoclonal antibodies (MoAbs) against EGFR (Sanchez-Ibarra et al., 2020). Initially all mCRC patients who failed the first line of chemotherapy were offered these agents. Subsequent research demonstrated that patients with tumours bearing the above mutations did not benefit from anti-EGFR MoAbs (Sartore-Bianchi et al., 2009). As a result, colorectal tumours are nowadays screened for the presence of these genetic variants and when present, patients are excluded from anti-EGFR MoAbs (ESMO guidelines). Evidently, there is a high clinical need for more of such predictive biomarkers. To find such biomarkers, the Centre for Personalized Cancer Treatment and the Hartwig Medical Foundation have initiated a nation-wide clinical study in which tumour biopsies were taken from metastases in patients with solid tumours, prior to starting a new line of treatment[4, 5] (Priestley et al., 2019). This has resulted in a large database with Whole Genome Sequencing data of metastases and outcome to treatments given, comprising data from almost 7,000 patients[6]. This database is accessible to researchers worldwide and will hopefully result in the discovery of other genetic markers with clinical utility.

Next to predictive markers, another important means to reduce overtreatment is detecting early markers of treatment failure (Smerage et al., 2014). Generally, in most cancer types, treatment is continued until objective progression is displayed by radiological assessments, which are often done at 2–3 months interval. Simpler methods executed at shorter time intervals can display resistance at an earlier time point by which overtreatment can be avoided. In this respect, liquid biopsies hold great promise and several studies are ongoing to assess their value as an early marker of response and to guide treatment.

Overtreatment does not limit to patients with failed therapy. It also affect patients who receivedurable benefit from treatment when the treatment intensity or treatment duration is higher than necessary to achieve the therapeutic aim. Evidence is somewhat lacking recommended dose intensity or treatment duration (e.g., number of cycles). This issue has long been recognized given many studies in the past, for example, comparing three *versus* four cycles of chemotherapy consisting of bleomycin, etoposide, cisplatin in patients with good-prognosis metastatic testicular cancer (de Wit et al., 2001) or shorter periods of adjuvant trastuzumab in primary breast cancer patients (Earl et al., 2019).

The same lack of evidence happens with costly new immunotherapies which are often administered until unacceptable toxicity or progression, whichever comes first, or for a maximum of 2 years. For example, monotherapy with MoAbs directed against PD-1 in advanced melanoma patients are given for 2 years without a strong rationale for this regimen. Several studies are ongoing to establish whether this treatment can be safely terminated in patients experiencing a confirmed response, which

4 https://www.hartwigmedicalfoundation.nl/.

5 https://www.cpct.nl/.

6 https://www.hartwigmedicalfoundation.nl/en/research-and-science/onderzoek/.

usually happens 6–9 months after treatment start, instead of prolonging therapy until 2 years consistent with the findings of clinical trials (Mulder et al., 2021). Another example is the SONIA study, in which CDK4/6 inhibitors have proven value when added to endocrine treatment in patients with hormone-receptor, HER2 negative metastatic breast cancer. It was, however, unknown whether CDK4/6 inhibitors should be applied in the first or the second line. In this randomised study, outcomes in terms of progression free survival and overall survival were similar between use in first line and second line. However, first line use was associated with 16.5 months longer treatment on CDK4/6 inhibitors, which led to a 42% increase in grade 3/4 toxicities and €180.000 higher costs per patient (Sonke et al., 2023). In other tumour types, similar studies are ongoing and although not all treatments can be shortened given the extensive heterogeneity in disease characteristics including treatment sensitivity, this is an important topic to explore (Lorigan and Eggermont, 2019; Waterhouse et al., 2020). Based on such studies, several guidelines already recommend shorter treatment periods (Keilholz et al., 2020; Sun et al., 2023).

2.3 Careful administration and avoidance of spillage: sustainable treatment and solid hospital finance

For convenience reasons, pharmaceutical companies have often justified their decision to change from weight-base dosing to fixed dose regimens. For example, pembrolizumab, in initial studies, a weight-base dose of 2 mg/kg/dose Q3W was demonstrated to be effective. This regimen was later adjusted to a fixed dose of 200 mg Q3W, which indicated there is no dose reduction recommended even if patient's weight is lower than the average adult weight. However, it was demonstrated that weight-based dosing of pembrolizumab was equally effective and safe (Bayle et al., 2019). This published pharmacokinetic model (Bayle et al., 2019) has validated that a dosing regimen of 2 mg/kg Q3W could equate to 4 mg/kg/dose Q6W (with 400 mg as maximum dose) (Diekstra et al., 2020). Within our own clinical setting, as was described in Malmberg et al., the modified dose of 4 mg/kg Q6W with a maximum dose of 400 mg and a dose rounding margin of 10%, has not only provided effective and safe treatment for our patients, but also prevented potential overdose (Malmberg et al., 2022) and reduced costs by 22% (in 2022). This weight-based dose-capping strategy can be implemented for more expensive cancer treatments such as nivolumab and other immune checkpoint inhibitors (Hall et al., 2020).

Apart from efficient dosing, medicine spillage offers further cost saving benefits. Cancellation of intravenous (IV) therapy, which has been prepared in advance, due to toxicity of disease progression can lead to wastage. Therefore, Erasmus MC schedules patients undergoing the same treatment on the same day. In this way, when patients have to cancel on short notice, the therapy can be given to another patient. Another example, introduced by Radboud UMC in the Netherlands, is the reduction of spillage of oral oncology drugs. When patients with a progressive course of their disease stop their oral therapy, large quantities of oral anticancer drugs may be left unused. Collecting and re-dispensing these unused drugs can save money and contribute to achieve sustainability goals (Smale et al., 2021). Therefore, oncologists should find a balance between prescribing adequate medication supply for patients' home and the risk of destroying unused surplus when therapy change is required.

2.4 Local production to save costs on trial medication and medical treatment

Many commercialised cancer drugs were discovered by researchers of university hospitals. The first prototypes of these potential drugs, used for preclinical testing, are often manufactured inside this hospital. For instance, in 2004, the first European clinical studies on solid tumours with CAR-T cells were performed at Erasmus MC with an in-house product (Lamers et al., 2006). The same goes for lutetium-labelled octreotide—Lu-177-DOTATATE –, a very effective radiopharmaceutical therapy for patients with gastroenteropancreatic neuroendocrine tumours (GEP-NET), which was discovered at Erasmus MC. For over 20 years it has been successfully administered to large groups of patients within the Netherlands and abroad (Strosberg et al., 2017). In 2017, this treatment was registered in Europe, after an industry-sponsored phase III study (Strosberg et al., 2017). In 2019, at market entry in the Netherlands, the drug price was substantially higher than our own manufacturing costs at that time. Negotiations between health insurers and the pharmaceutical company unfortunately resulted in the withdrawal of this treatment from the Dutch market in 2020. Currently, Erasmus MC produces this drug for its own patients,and, in 2022, reduced costs by 42% compared to the costs of the licensed product. Similarly, we recently started producing Lu-177-PSMA for patients with prostate specific membrane antigene (PSMA)- positive metastatic castration-resistant prostate cancer (mCRPC). We expect costs of the licensed product when it enters the Dutch market will be higher than our own pharmacy preparation.

Erasmus MC is not the only Dutch university hospital which makes effort to provide its patients with affordable medicines. Amsterdam UMC has started to produce chenodeoxycholic acid (CDCA) capsules through in-house production—a drug for treatment of the rare metabolic disorder cerebrotendinous xanthomatosis (CTX) which was prescribed off-label–, after the pharmaceutical company had registered this drug in 2017 and increased the price 500 fold (Polak et al., 2021). These examples demonstrate that university hospitals are capable of successfully manufacturing medicines for their patients at lower costs and should be further explored internationally.

2.5 Affordable pricing: smart procurement and novel pricing models

In the Netherlands, medicines can only be procured by hospitals after they have been granted market authorization at a national or European level and have obtained a reimbursement status. Generally, purchase prices are being established in negotiations between pharmaceutical companies and hospitals

in which the former has an incentive to aim for the highest price in order to create shareholder value and the latter aims for the lowest price given a restricted healthcare budget. In an attempt to negotiate prices to the lowest possible level, the Dutch university hospitals cooperate in a joint procurement board[7]. However, focusing solely on the lowest price is not a sustainable solution as this strategy may reduce the number of pharmaceutical suppliers and therefore diminish competition to a, in the worst case, monopoly position. Moreover, having fewer suppliers put the supply chain at risk during potential medicine shortages. Focussing on price may be more favourable in the short term, but in the long run it is more beneficial to secure competition. In 2020, Erasmus MC, together with several health insurers, has decided to not always select the cheapest supplier in order to foster competition.

While negotiating prices is an effective way of lowering expenditure on pharmaceuticals, the real question is whether or not buyers are paying a fair price, i.e., being delivered value-for-money. Even though call for transparency on the costs of drugs increases, pharmaceutical companies are reluctant to disclose how prices are being established. In response to that, researchers from Erasmus University Rotterdam proposed and successfully applied a novel pricing model to calculate a fair price for oncology drugs which displays the cost-based prices (including R&D costs and profit margin) are substantially lower than the list price (Uyl-De Groot and Löwenberg, 2018; Thielen et al., 2022). Researchers from Amsterdam UMC created an alternative pricing model for establishing the price for a repurposed drug—mexiletine—using a recent European drug-pricing model[8] as a framework to include actual costs incurred (van den Berg et al., 2021).

2.6 Future research and activities

We touched upon several successful interventions and we will continue to explore other interventions such as registration of in-house discovered and developed drugs, raising awareness on cost-effective prescribing, developing start and stop criteria, and research on less intense treatment schemes (e.g., lowering dose per administration, extending intervals between administrations, shortening treatment duration and boosting of medication).

Regarding clinical studies, researchers from university hospitals can compare the eligibility criteria in the study with patient characteristics in daily life and adapt them accordingly. Moreover, researchers and clinicians have access to real-world data that can be used in the reassessment of clinical efficacy and cost-effectiveness of cancer drugs after market approval. We will continue to expand our efforts to reduce spillage by optimizing shelf life of drugs in stock and pooling. Finally, we must discuss with our patients the possibility of non-treatment and focus on quality of life instead of quantity of life.

Most importantly, a strong collaboration between the hospital pharmacy department and medical departments is the key to successful intervention implementation.

We anticipate even more opportunities for (university) hospitals to combat the rising costs of cancer drugs, if we collaborate on a European level. We can start by sharing best practices on precision dosing and avoidance of spillage, collaborate on promising new technologies such as ATMPs and strive collectively for fair prices.

To overcome legal barriers, we should collaborate on adapting European legislation to be more open to self-manufacturing of medicines, and find innovative ways to jointly purchase expensive (cancer) drugs. Lastly, explore solutions—both on an European and national level–for legal issues regarding off-label prescribing (e.g., with precision dosing of pembrolizumab) is essential.

3 Conclusion

Our aim was to inspire other hospitals to take action. Here, we have focused on several strategies to prevent overtreatment and to minimise costs of expensive anti-cancer drugs such as clinical research on identification of predictive markers and, precision dosed administration of drugs, local manufacturing and effective procurement methods. These strategies illustrate potential contribution of (university) hospitals to the reduction of expenditure growth on cancer drugs, while maintaining access, effectiveness and safety.

We urge other hospitals to review their own activities throughout the drug life cycle, collaborate on overcoming barriers and help contributing to a sustainable and affordable healthcare system.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AD: Conceptualization, Visualization, Writing–original draft, Writing–review and editing. RL: Writing–original draft, Writing–review and editing. MH: Writing–review and editing. HK: Supervision, Writing–original draft, Writing–review and editing. SS: Supervision, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

7 Inkoopcombinatie Ziekenhuis Apotheken Academische Ziekenhuizen (IZAAZ) NFU.

8 AIM European Fair Price Calculator for Medicines: Home: Fair Pricing Calculator.

Acknowledgments

The authors wish to thank Ngoc Hong (Wendy) Tan, clinical pharmacist and PhD candidate at the Dept. of Hospital Pharmacy, Erasmus MC, Rotterdam, the Netherlands for her valuable comments on English style and grammar.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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frontiers | Frontiers in Pharmacology

TYPE Opinion
PUBLISHED 29 August 2023
DOI 10.3389/fphar.2023.1241979

OPEN ACCESS

EDITED BY
Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani,
CZ Health Insurance, Netherlands

REVIEWED BY
Karina Meijer,
University Medical Center Groningen, Netherlands
Simone Koole,
ONVZ, Netherlands

*CORRESPONDENCE
Vinay Prasad,
vinayak.prasad@ucsf.edu

RECEIVED 18 June 2023
ACCEPTED 21 August 2023
PUBLISHED 29 August 2023

CITATION
Walia A and Prasad V (2023), Extended anticoagulation for VTE: what evidence justifies it?
Front. Pharmacol. 14:1241979.
doi: 10.3389/fphar.2023.1241979

Extended anticoagulation for VTE: what evidence justifies it?

Anushka Walia[1] and Vinay Prasad[2]*

[1]School of Medicine, University of California, San Francisco, San Francisco, CA, United States, [2]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, United States

KEYWORDS

anticoagulation, venous thromboembolism, pulmonary embolism, deep venous thromboembolism, clot

Opinion

Venous thromboembolism (VTE), which includes pulmonary embolism and deep vein thrombosis, is associated with significant morbidity and mortality. The cornerstone of VTE treatment is anticoagulation with direct oral anticoagulants (DOACs), vitamin K antagonists, or heparin. Acute VTE is treated with 5–10 days of active therapy followed by extended anticoagulation of various durations. For VTE with known transient provoking factors, anticoagulation is discontinued after 3–6 months (Ortel et al., 2020). In the case of unprovoked VTE, anticoagulation is typically continued indefinitely. These guidelines are based on clinical studies demonstrating a persistent risk of VTE recurrence in patients with first unprovoked VTE, as well as loss of prophylactic effect once treatment is stopped (Couturaud et al., 2015). However, direct advantage of indefinite over short-term anticoagulation has not been assessed in randomized clinical trials (RCTs), and must be carefully weighed against the risk of major bleeding events. In this commentary, we explore the challenges of assessing the true value of indefinite anticoagulation in patients with first time VTE without identifiable provoking risk factor.

Provoked vs. unprovoked VTE

Distinguishing between provoked and unprovoked VTEs is imperfect and often challenging. 2016 recommendations by the International Society on Thrombosis and Haemostasis (ISTH) define transient provoking factors for VTE as those associated with a "greater than 3-fold increased risk of first VTE or half the risk of recurrent VTE after stopping anticoagulant therapy" (Kearon et al., 2016). Provoking factors range from known major triggers such as surgery and extended hospitalization to minor triggers like acute medical illness or estrogen therapy. Because identification of risk factors is often contingent on history and clinician judgement, the distinction between provoked and unprovoked VTEs is not black or white and definitions differ by study (Iorio et al., 2010). Yet, it determines whether a patient will receive therapy for a few months or the remainder of their life.

There is limited data comparing long-term VTE recurrence rates among patients with provoked and unprovoked VTEs, and results have been mixed. The prospective GARFIELD-VTD study, which included 10,207 patients with VTE worldwide, compared outcomes in the presence or absence of transient provoking factors (Ageno et al., 2021). No difference in rates of recurrent VTE or mortality was found between provoked and unprovoked groups (4.4 vs. 2.9 per 100 person-years and 3.7 vs. 3.4 per 100 person-years respectively). This may be partially due to the longer duration of anticoagulation in the unprovoked group, with 51.5% of patients with unprovoked VTE and 36.7% of patients with transient provoking factors remaining on anticoagulation at 12 months. Iorio et al. found that the 24-month VTE

recurrence rate after stopping anticoagulation was 2.3-fold higher in patients with unprovoked first VTE than patients with VTE provoked by a transient risk factor (Iorio et al., 2010). Recurrence rates varied depending on whether transient provoking factors were surgical or non-surgical. A 2003 study on recurrent VTE by Baglin et al. found similar results (Baglin et al., 2003). Still, it is not clear whether long term outcome differences between risk groups are high enough to warrant such divergent treatment approaches.

Clinically unsuspected or "incidental" VTEs represent another major clinical challenge, as their clinical significance has never been proven. The threshold to detect clots is lower today than in the past, with VTEs commonly found on routine CT scans. Rates of clinically unsuspected VTEs are as high as 3.3% in patients referred for chest CT according to one meta-analysis, and detection largely depends on the skill of the radiologist (Chiu and O'Connell, 2017). Despite the increased rates of diagnosis of VTEs over the years, the mortality rate has not increased. Current guidelines recommend the same treatment for clinically suspected and unsuspected VTEs, based on retrospective data suggesting an association between incidental VTEs and increased risk of future events. A recent multicenter prospective trial by examined 90-day VTE recurrence rates in patients with isolated subsegmental pulmonary embolism (SSPE) managed without anticoagulation (Le Gal et al., 2022). They found that despite 8 recurrence events among 266 patients, no patients had a fatal recurrent pulmonary embolism. The clinical benefit of anticoagulation in patients with SSPE is unclear, and the same may be true for other incidental VTEs.

Recurrent VTE vs. major bleeding

Anticoagulation trials typically use a primary endpoint of VTE recurrence and a safety endpoint of bleeding. The clinical decision of how long to anticoagulate rests on a precarious balance between these possibilities, which may not be equivalent risks. While recurrent VTE may carry significant mortality risk, the case fatality rate (CFR) for major bleeding has been demonstrated to be higher than the CFR for VTE recurrence among patients receiving anticoagulants. One metanalysis of 68 clinical studies, of which 56 were RCTs, found CFRs of major bleeding and recurrent VTE to be comparable during 6 months of anticoagulation (Carrier et al., 2010). However after the initial 3–6 months of treatment, the CFR of recurrent VTE was about 3 times lower than that of major bleeding. In a study on the RIETE database, a prospective registry for patients treated for VTE, CFRs of recurrent VTE and major bleeding were 12.1% and 19.7% respectively during anticoagulant therapy (Lecumberri et al., 2013). While the CFR of recurrent VTE decreased from 16.1% during the first 3 months of treatment to 2.0% after 3 months, the CFR of major bleeding only changed from 20.2% to 18.2%.

Because bleeding risk typically increases with age while rates of VTE recurrence peak immediately after the first event and drop to a plateau after a few years, the benefit/risk ratio of anticoagulation may decline over time (Bounameaux and Perrier, 2008). Importantly, bleeding risk may be underestimated in clinical trial populations, as real-world patients are older and have greater comorbidities, including higher rates of reduced renal function—a risk factor for major bleeding (Geldhof et al., 2014).

While physicians may halt anticoagulation in patients at high risk of major bleeding, this risk is difficult to assess. None of the available bleeding risk assessment tools have been validated in clinical trials, and several studies have demonstrated that they have poor predictive value for patients with VTE (Vedovati et al., 2020). Partly due to the inability to predict major bleeding, it is unclear whether to prioritize the risk of VTE recurrence or the risk of hemorrhage. Although clinicians have traditionally leant towards the former, long-term data comparing mortality associated with VTE vs. hemorrhage is necessary to make this decision. The risk-benefit profile of anticoagulants must also be re-evaluated in the era of DOACs, which have become first-line for most patients with VTE over vitamin K antagonists.

Mortality and RCTs

Whether anticoagulation yields improvements in patient-centered outcomes such as survival and quality of life is unclear. Although CFRs can provide some information on mortality, answering this question conclusively requires adequately powered RCTs with long follow-up periods. A Cochrane metanalysis of 11 clinical studies comparing short-term and prolonged treatment with vitamin K antagonists found that prolonged therapy was associated with a strong reduction in recurrent VTEs (Middeldorp et al., 2014). However, notably, no significant reduction in mortality in those who received shorter treatment was found (RR 0.89, 95% Cl 0.66 – 1.21, $p = 0.46$) but prolonged treatment was associated with a substantially increased bleeding complications (RR 2.60, 95% Cl 1.51 – 4.49). In addition, their analysis did not demonstrate "rebound" hypercoagulability post-therapy (Cundiff, 2008) that leads to fear of discontinuing treatment.

RCTs of anticoagulants have not provided information on the optimal duration of therapy for VTE prophylaxis after first-time unprovoked VTE. One trial compared outcomes 6 months of oral anticoagulant therapy with indefinite anticoagulation in 227 patients with a second episode of VTE (Schulman et al., 1997). During 4 years of follow-up, authors found a significantly increased risk of recurrent VTE in the 6-month group but no difference in mortality between the two groups. In fact, no cases of fatal pulmonary embolism were confirmed. The relative risk of major hemorrhage in the 6-month group compared to the indefinite anticoagulation group was 0.3, and 3 hemorrhages in total were fatal.

No trial has directly compared 3–6 months of anticoagulation with indefinite treatment after first-time unprovoked VTE, and the longest period of treatment in the extended arm of an RCT has been around 4 years. Despite lack of evidence, patients may remain on anticoagulant therapy for decades.

Conclusion

The secondary anticoagulation strategy for unprovoked VTE presents several challenges. Differentiating unprovoked and provoked VTE is often subjective and many cases fall in a gray area between these categories. Prolonged anticoagulation carries a

persistent high risk of major bleeding that may be poorly estimated and comparable with the risk of recurrent VTE. Data comparing lifetime risks of bleeding and recurrent VTE is lacking. In addition, RCTs have not established a survival or quality of life benefit of indefinite anticoagulation or directly compared indefinite and short-term therapy. With an aging population and increased PE detection capability, rates of anticoagulation are expected to increase, adding costs to our healthcare system.

The evidence base for indefinite thromboprophylaxis must be increased. Until we have more data, a patient-centered approach that evaluates individual risk factors and preferences should guide anticoagulation after VTE.

Author contributions

Both authors contributed to this editorial's conception and implementation. The first draft of the manuscript was written by AW with input from VP. All authors contributed to the article and approved the submitted version.

Conflict of interest

Disclosure: VP's Disclosures. (Research funding) Arnold Ventures (Royalties) Johns Hopkins Press, Medscape, and MedPage (Honoraria) Grand Rounds/lectures from universities, medical centers, non-profits, and professional societies. (Consulting) UnitedHealthcare and OptumRX. (Other) Plenary Session podcast has Patreon backers, YouTube, and Substack.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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TYPE Original Research
PUBLISHED 31 August 2023
DOI 10.3389/fphar.2023.1238009

OPEN ACCESS

EDITED BY
Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani,
CZ Health Insurance, Netherlands

REVIEWED BY
Anushka Walia,
University of California San Francisco, United States
Jolanda Boer,
De, National Healthcare Institute (ZIN), Netherlands

*CORRESPONDENCE
Qundan Wu,
365885958@qq.com
Ruijia Chen,
ruijiachen503@163.com

RECEIVED 10 June 2023
ACCEPTED 27 July 2023
PUBLISHED 31 August 2023

CITATION
Huang Y, You M, Wu Q and Chen R (2023), Cost-effectiveness analysis of zolbetuximab plus mFOLFOX6 as the first-line treatment for CLDN18.2-positive, HER2-negative advanced gastric or Gastroesophageal Adenocarcinoma. *Front. Pharmacol.* 14:1238009. doi: 10.3389/fphar.2023.1238009

Cost-effectiveness analysis of zolbetuximab plus mFOLFOX6 as the first-line treatment for CLDN18.2-positive, HER2-negative advanced gastric or Gastroesophageal Adenocarcinoma

Yufan Huang[1], Maojin You[1], Qundan Wu[2]* and Ruijia Chen[3]*

[1]Department of Pharmacy, Mindong Hospital Affiliated to Fujian Medical University, Ningde, Fujian, China, [2]Department of Pharmacy, Quanzhou Skin Disease Prevention and Treatment Hospital, Quanzhou, Fujian, China, [3]Department of Pharmacy, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, Fujian, China

Background: The SPOTLIGHT trial demonstrated that zolbetuximab plus mFOLFOX6 (ZOL-FO) as a first-line regimen compared with placebo plus mFOLFOX6 (PLB-FO) conferred clinical benefits to patients with CLDN18.2-positive, HER2-negative advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. However, due to the high cost of zolbetuximab, whether ZOL-FO is cost-effective compared with PLB-FO is unclear. This study aimed to evaluate the cost-effectiveness of ZOL-FO as a first-line treatment option for CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma from the perspective of the Chinese healthcare system.

Methods: Markov models with three different health states were developed to assess the cost-effectiveness of ZOL-FO as a first-line treatment option for CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma. Clinical efficacy data were obtained from the SPOTLIGHT trial; the drug's cost was calculated at national bid prices, and other costs and utility values were obtained from the published literature. Outcomes included total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). The model's robustness was verified using one-way sensitivity and probabilistic sensitivity analyses.

Results: The ZOL-FO group gained 1.64 QALYs at $87,746.35, while the PLB-FO group gained 1.23 QALYs at $11,947.81. The ICER for ZOL-FO *versus* PLB-FO was $185,353.28 per QALY gained. The parameters exerting an important impact on the model results were the price of zolbetuximab, body surface area, and progression-free survival utility. At a willingness-to-pay threshold of $38,201/QALY, ZOL-FO had a 0% probability of cost-effectiveness compared with PLB-FO.

Conclusion: From the perspective of the Chinese healthcare system, ZOL-FO is unlikely to be cost-effective as the first-line treatment option for CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma.

KEYWORDS

cost-effectiveness, zolbetuximab, CLDN18.2-positive, HER2-negative, gastric or gastroesophageal adenocarcinoma, first-line treatment

1 Introduction

Gastric cancer (GC), with the fourth highest mortality rate and the fifth highest incidence among all malignant diseases, is a common cancer that threatens human health (Sung et al., 2021). China is at a high risk of GC, with more than 6.7 million newly diagnosed cases and approximately 5 million new deaths each year, accounting for 42% and 45% of the global cases, respectively (Chen et al., 2016). Nearly 90% of GC patients already develop metastases by the time they are first diagnosed (Zeng et al., 2018), and their prognoses are poor, with a 5-year survival rate of only 5% (Shu et al., 2022). The cancer of the gastroesophageal junction can also be classified as GC (Smyth et al., 2020). In gastric or gastroesophageal junction (G/GEJ) cancers, more than 90% of the histological types are adenocarcinomas (Ajani et al., 2017). The standard first-line treatment regimen for advanced G/GEJ adenocarcinoma is platinum combined with fluorouracil therapy (Wang et al., 2021); however, this chemotherapy has unsatisfactory efficacy, with a median survival of less than 1 year (Shitara et al., 2023). In recent years, although chemotherapy plus trastuzumab or nivolumab has been used as first-line treatment for advanced G/GEJ adenocarcinoma with HER-2-positive or high programmed death-ligand 1 (PD-L1) co-positive score, respectively (Bang et al., 2010; Jiang et al., 2022), the survival benefit remains low and the disease may rapidly recur or progress (Nakamura et al., 2021; Myer et al., 2022), necessitating the need to explore new molecular targets (Salati et al., 2023).

Claudin 18.2 (CLDN18.2), the tight junction protein, is a promising target for the treatment of G/GEJ adenocarcinoma (Sahin et al., 2008). Zolbetuximab, a chimeric IgG1 monoclonal antibody, targets and binds to CLDN18.2, thus inducing cell death in CLDN18.2-positive G/GEJ adenocarcinoma (Sahin et al., 2018). A recent phase III clinical trial (SPOTLIGHT) evaluated the efficacy and safety of zolbetuximab plus mFOLFOX6 (modified folinic acid, fluorouracil, and oxaliplatin regimen, ZOL-FO) as the first-line treatment of CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic G/GEJ adenocarcinoma (Shitara et al., 2023). The results showed that ZOL-FO significantly improved the overall survival (OS) and progression-free survival (PFS) of patients with CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma compared with placebo plus mFOLFOX6 (PLB-FO), giving new hope for patients with advanced G/GEJ adenocarcinoma.

Although ZOL-FO provides clinical benefits for patients with CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma, its high cost limits its widespread use. Therefore, the cost-effectiveness of ZOL-FO must be evaluated by pharmacoeconomic methods to assess the clinical benefits and potential financial consequences of ZOL-FO for patients with advanced G/GEJ adenocarcinoma and determine the rationale for its widespread use in the future. To the best of our knowledge, the economics of ZOL-FO has not been evaluated. This study estimates the cost-effectiveness of ZOL-FO as a first-line regimen for the treatment ofCLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma compared with PLB-FO from the perspective of the Chinese healthcare system based on the results obtained from the SPOTLIGHT trial (Shitara et al., 2023). This study was designed according to the Comprehensive Health Economic Assessment Reporting Standards 2022 (CHEERS 2022) (Husereau et al., 2022) (Supplementary Table SA).

2 Methods

2.1 Model construction

Markov models were developed using TreeAge Pro 2022 (TreeAge Software, Williams-town, MA, United States) to estimate the cost and effectiveness of ZOL-FO compared with PLB-FO for patients withCLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma. The model contains three different health states, that is, PFS, progressive disease (PD), and death, which are mutually exclusive (Figure 1). We assumed that all patients entered the model with PFS and then as the Markov model was run, patients either remained in their current health state or progressed to a new health state but were not allowed to return to their previous health state. The length of each cycle in the model was 42 days. The model duration was 110 cycles (approximately 12.7 years), which was determined by the expected time to death kept at 99% of the hypothetical patients. The background mortality rate of China in 2022 was considered in the model (National Bureau of Statistics of China, 2023). The output of the model included total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). According to the China Guidelines for Pharmacoeconomic Evaluations, we used three times China's GDP *per capita* in 2022 ($38,201/QALY) as the willingness-to-pay (WTP) threshold, and if the ICER was below our predefined WTP threshold, the treatment option was considered cost-effective. Economic analyses were based on published randomized clinical trials and mathematical models. As a result, institutional review board or ethics committee approval was not necessary for this study.

2.2 Clinical data and transition probability

The survival benefit and safety data of our study were based on the results of the SPOTLIGHT trial (Shitara et al., 2023). Patients in this trial were distributed across 215 centers in 20 countries worldwide and had to meet the following criteria: 1) ≥18 years of age; 2) CLDN18.2 positive and HER2 negative; 3) previously untreated locally advanced unresectable or metastatic G/GEJ adenocarcinoma; 4) Eastern Cooperative Oncology Group performance status score of 0 or 1, and 5) adequate organ function.

These patients were randomly assigned to either the ZOL-FO or PLB-FO group; those in the ZOL-FO group received zolbetuximab 800 mg/m^2 (cycle 1, day 1), followed by 600 mg/m^2 (cycle 1, day 22, and days 1 and 22 of subsequent cycles), plus mFOLFOX6 (folinic acid 400 mg/m^2; fluorouracil 2,800 mg/m^2; oxaliplatin 85 mg/m^2; days 1, 15, and 29 of each cycle). Patients in the PLB-FO group received a placebo plus mFOLFOX6. All patients receiving four

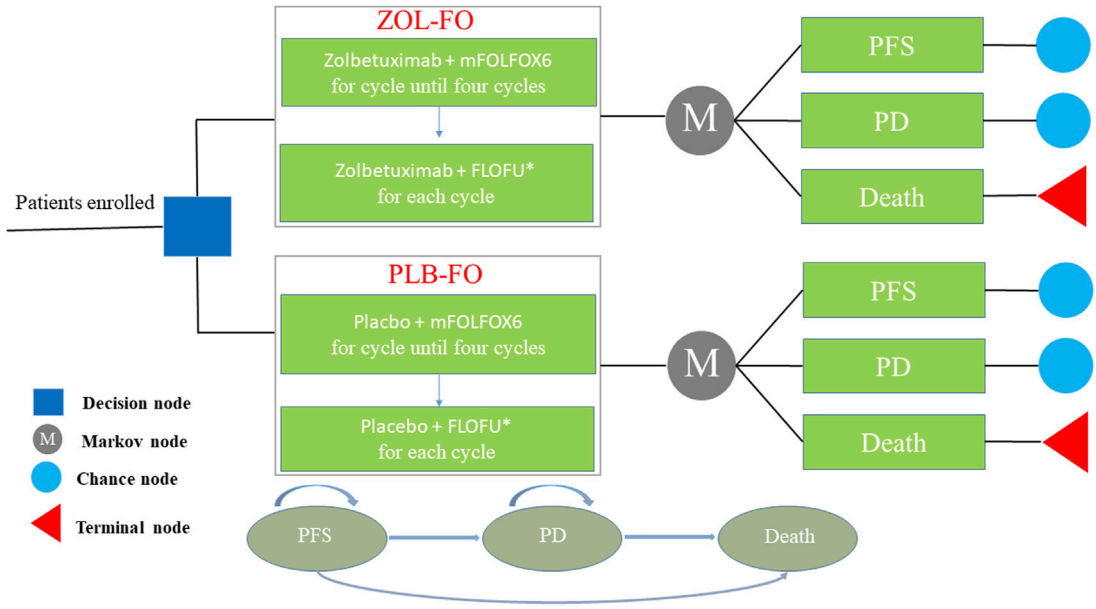

FIGURE 1
The Markov model simulating outcomes for the CAPSTONE-1 trial. All patients started with PFS state and received treatment with ZOL-FO or PLB-FO. FLOFU*, folinic acid and fluorouracil at the discretion of the investigator; PD, progressive disease; PFS, progression-free survival; PLB-FO, placebo plus mFOLFOX6; ZOL-FO, zolbetuximab plus mFOLFOX6.

TABLE 1 Relevant parameters of the survival distribution.

Parameters	Value	Source
Loglogistic survival model of PFS		
PLB-FO	Scale = 0.1091424, Shape = 1.892484	Shitara et al. (2023)
ZOL-FO	Scale = 0.08578011, Shape = 1.596389	Shitara et al. (2023)
Log-logistic survival model of OS		
PLB-FO	Scale = 0.06858134, Shape = 1.943703	Shitara et al. (2023)
ZOL-FO	Scale = 0.05460772, Shape = 1.620319	Shitara et al. (2023)

OS, overall survival; PFS, progression-free survival; PLB-FO, placebo plus mFOLFOX6; ZOL-FO, zolbetuximab plus mFOLFOX6.

cycles of treatment without disease progression continued zolbetuximab or placebo plus folinic acid and fluorouracil at the discretion of the investigator until disease progression or onset of toxic effects. Based on the SPOTLIGHT trial (Shitara et al., 2023), we assumed that when patients showed disease progression, a subset received chemotherapy, immunotherapy, or targeted therapy, and others received the best supportive care. All patients received the best supportive care after the failure of second-line therapy.

The transition probabilities between different health states were estimated based on the Kaplan-Meier survival curves from the SPOTLIGHT trial (Shitara et al., 2023). First, OS and PFS data points from Kaplan-Meier survival curves for both treatment groups were extracted using GetData Graph Digitizer (version 1.2), a software that digitizes images. Then, according to the method described by Guyot et al. (Guyot et al., 2012), the R software (version 4.2.0) was used to reconstruct Kaplan-Meier survival curves and extrapolate long-term clinical outcomes beyond the follow-up time, using the extracted data points. Various distribution functions, including exponential, Weibull, log-normal, and log-logistic, were assessed to identify the most suitable survival function based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Lower AIC and BIC values indicated a better fit (Ishak et al., 2013; Williams et al., 2017). The AIC and BIC values for these distribution functions are presented in Supplementary Figure SB. Ultimately, the log-logistic distribution function was determined to best fit the PFS and OS data for both treatment groups (Table 1, Supplementary Figure SA). Accordingly, the time-dependent jump probability for each cycle in the model was calculated using the following equation: $1-\{[1+\lambda t\gamma]/[1+\lambda(t+1)\gamma]\}$ (t, Current model cycle; λ, scale parameter; γ, shape parameter) (Diaby et al., 2014).

2.3 Costs and utilities

Only direct medical costs were considered, including costs of drugs, routine follow-up, best supportive care, tests, terminal care in end-of-life, and management of grade 3 or higher adverse reactions

10.3389/fphar.2023.1238009

TABLE 2 Basic parameters of the input model and the range of sensitivity analyses.

Variable	Base value	Range		Distribution	Source
		Min	Max		
ZOL-FO group: Incidence of AEs (%)					
Nausea/Vomiting	32.26	25.81	38.71	Beta	Shitara et al. (2023)
Neutropenia	28.32	22.65	33.98	Beta	Shitara et al. (2023)
Anemia	8.60	6.88	10.32	Beta	Shitara et al. (2023)
Neutrophil count decrease	24.73	19.78	29.68	Beta	Shitara et al. (2023)
Fatigue	6.09	4.87	7.31	Beta	Shitara et al. (2023)
PLB-FO group: Incidence of AEs (%)					
Nausea/Vomiting	12.23	9.78	14.68	Beta	Shitara et al. (2023)
Neutropenia	23.38	18.71	28.06	Beta	Shitara et al. (2023)
Anemia	9.35	7.48	11.22	Beta	Shitara et al. (2023)
Neutrophil count decrease	24.82	19.86	29.78	Beta	Shitara et al. (2023)
Fatigue	5.04	4.03	6.04	Beta	Shitara et al. (2023)
Costs ($)					
Folinic acid (100 mg)	17.54	14.03	21.05	Gamma	Yao (2023)
Fluorouracil (100 mg)	1.78	1.42	2.14	Gamma	Yao (2023)
Oxaliplatin (100 mg)	59.82	47.86	71.78	Gamma	Yao (2023)
Zolbetuximab (100 mg)	258.20	206.56	309.84	Gamma	Yao (2023)
Paclitaxel (30 mg)	10.10	8.08	12.12	Gamma	Yao (2023)
Nivolumab (100 mg)	1374.44	1099.55	1649.33	Gamma	Yao (2023)
Best supportive care per cycle	182.23	145.78	218.68	Gamma	Zhang et al. (2021a)
Routine follow-up per cycle	73.72	58.98	88.46	Gamma	Zhang et al. (2021b)
Tests per cycle	357.34	285.87	428.81	Gamma	Liu et al. (2022)
Terminal care in end-of-life	1489.51	1191.60	1787.41	Gamma	Liu et al. (2023)
Nausea/Vomiting	101.15	80.92	121.38	Gamma	Zhan et al. (2022)
Neutropenia	454.26	363.41	545.11	Gamma	Liu et al. (2022)
Anemia	336.63	269.30	403.96	Gamma	Zhan et al. (2022)
Neutrophil count decrease	454.26	363.41	545.11	Gamma	Liu et al. (2022)
Fatigue	115.40	92.32	138.48	Gamma	Wu et al. (2012)
Utility value					
PFS	0.797	0.638	0.956	Beta	Shu et al. (2022)
PD	0.577	0.462	0.692	Beta	Shu et al. (2022)
Disutility due to AEs					
Nausea/Vomiting	−0.12	−0.10	−0.14	Beta	Nafees et al. (2017)
Neutropenia	−0.20	−0.16	−0.24	Beta	Nafees et al. (2017)
Anemia	−0.07	−0.06	−0.08	Beta	Cai et al. (2021)
Neutrophil count decrease	−0.20	−0.16	−0.24	Beta	Nafees et al. (2017)
Fatigue	−0.07	−0.06	−0.08	Beta	Nafees et al. (2017)
Discount rate	0.05	0.00	0.08	Fixed	Liu (2020)
Weight (kg)	65	52.00	78.00	Normal	Liu et al. (2022)
Body surface area (m^2)	1.72	1.38	2.06	Normal	Liu et al. (2022)
The proportion of subsequent anticancer therapies (%)					
ZOL-FO group					
Chemotherapy	22.97	18.38	27.56	Beta	Shitara et al. (2023)
Targeted therapies	12.36	9.89	14.83	Beta	Shitara et al. (2023)
Immunotherapies	9.19	7.35	11.03	Beta	Shitara et al. (2023)
PLB-FO group					
Chemotherapy	24.11	19.29	28.93	Beta	Shitara et al. (2023)
Targeted therapies	12.06	9.65	14.47	Beta	Shitara et al. (2023)
Immunotherapies	9.93	7.94	11.92	Beta	Shitara et al. (2023)

AE, adverse event; PD, progressive disease; PFS, progression-free survival; PLB-FO, placebo plus mFOLFOX6; OS, overall survival; ZOL-FO, zolbetuximab plus mFOLFOX6.

with an incidence greater than 5% considered (Table 2). The costs of these drugs were obtained from the national tender price. However, zolbetuximab is not yet available in the market, so we used the price of nivolumab in China, an immune checkpoint inhibitor recommended for first-line treatment of GC, as the reference price for zolbetuximab (converted to the cost needed for a single treatment), according to the method of Weng et al. (Weng et al., 2020). Other costs were obtained from published literature and were adjusted to costs in 2022 based on the China Medical Price Index (National Bureau of Statistics of China, 2023). All costs were converted to US dollars at the average US-China exchange rate in 2022 (1$ = 6.73 RMB). To calculate the dose administered to patients, we assumed that the patients had a body weight of 65 kg and a body surface area of 1.72 m^2(Liu et al., 2022; Shu et al., 2022). The PFS and PD in this study were obtained from published Chinese literature because relevant quality-of-life data for patients were not available from the SPOTLIGHT trial (Table 2). To reduce the impact of using the same utility in the ZOL-FO and PLB-FO groups, we also considered the disutility of adverse reactions of grade 3 and above with an incidence of >5% in our model. We discounted the costs and health utilities at 5% per year according to the China Guidelines for Pharmacoeconomic Evaluations (Liu, 2020).

2.4 Sensitivity analysis

To examine the model's robustness and the uncertainty in the parameter estimates, we performed one-way and probabilistic sensitivity analyses. To perform a one-way sensitivity analysis, we adjusted each parameter within a given range (Table 2) to determine the effect of these changes on the ICER. The ranges of variation for all parameters were 95% confidence intervals from the literature and were assumed at ±20% of the baseline values in the absence of data. The lower and upper bounds of the discount rate were set at 0% and 8%, respectively. The results of the one-way sensitivity analysis are presented as tornado plots. We assigned all parameters to the appropriate distributions (Table 2) in the model and performed a probabilistic sensitivity analysis (PSA) with 1,000 Monte Carlo simulations to determine the effect of simultaneous changes in multiple parameters on the model results. The results of PSA are represented as scatter plots. We explored the effect of different prices on varying cost-effective results of ZOL-FO by continuously changing the price of zolbetuximab.

2.5 Subgroup analysis

To assess the impact of subgroups with different baseline characteristics on the model results, we performed exploratory subgroup analysis. Due to the lack of sufficient data for each subgroup that could be used for survival analysis, according to the method described by Hoyle et al. (Hoyle et al., 2010), to facilitate subgroup survival extrapolation, we let all subgroups in the PLB-FO group use the same PFS and OS survival functions (log-logistic survival model) and used the subgroup-specific hazard ratio provided by the SPOTLIGHT trial (Table 3) to calculate ICERs and cost-effectiveness acceptability probabilities for each subgroup.

3 Results

3.1 Base case analysis

Our findings are expressed in terms of the total costs, QALYs, and ICERs (Table 4); 1.64 QALYs were achieved in the ZOL-FO group for $87,746.35. In the PLB-FO group, the survival benefit was 1.23 QALYs with an investment of $11,947.81. Compared with the PLB-FO, the mean incremental effectiveness and cost in the ZOL-FO were 0.41 QALYs and $75,798.54, respectively. The ICER for ZOL-FO *versus* PLB-FO was $185,353.28 per QALY gained. Therefore, in China, ZOL-FO is unlikely to be a cost-effective first-line treatment strategy for CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma compared with PLB-FO at a WTP threshold of $38,201/QALY.

3.2 Sensitivity analysis

The results of the one-way sensitivity analysis showed that in the tornado plot (Figure 2), the most important parameters that affected the model results were zolbetuximab's price, body surface area, and PFS utility. However, despite changing the values of these parameters, the ICER was always above our predetermined WTP threshold, implying that changes in parameter values could not change our model results. The variables having less impact on the results included the discount rate, PD utility, and the cost per cycle of tests. The PSA results are represented as scatter plots (Figure 3), and when the WTP threshold is $38,201/QALY, the probability that ZOL-FO is cost-effective compared to PLB-FO is 0%. When zolbetuximab's price (100 mg) drops below 18.33% of the predetermined price, i.e., below $43.72, ZOL-FO will be a cost-effective first-line treatment option for CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma.

3.3 Subgroup analysis

Compared with the PLB-FO group, all subgroups in the ZOL-FO group had ICERs above the WTP threshold of $38,201/QALY, with 0% probability of cost-effectiveness, except for the previous gastrectomy subgroup which had 0.2% (Table 3). Notably, in the PLB-FO group, more benefits and fewer costs were found for the subgroup with age >75 years, gastro-oesophageal junction cancer, and the current tobacco history, suggesting that these subgroups were not likely to be cost-effective with the ZOL-FO regimen; it is important to interpret these results cautiously due to the limited sample enrollment.

4 Discussion

In the first-line treatment of advanced HER2-negative GC, the American Society of Clinical Oncology recommends the use of nivolumab plus chemotherapy for patients with PD-L1 CPS (Combined Positive Score) ≥5 in G/GEJ adenocarcinoma, and pembrolizumab plus chemotherapy for patients with PD-L1 CPS ≥10 in GEJ adenocarcinoma(Press et al., 2017; Shah et al.,

10.3389/fphar.2023.1238009

TABLE 3 Results of subgroup analyses.

Subgroup	PFS HR (95% CI)	OS HR (95% CI)	ICER ($/QALY)	Cost-effectiveness probability
Age(years)				
≤65	0.77 (0.58–1.02)	0.74 (0.56–0.98)	207832.26	0
>65	0.71 (0.49–1.04)	0.76 (0.53–1.09)	186178.39	0
≤75	0.74 (0.59–0.93)	0.71 (0.57–0.90)	171802.56	0
>75	0.96 (0.39–2.34)	1.32 (0.58–3.00)	—	—
Sex				
Male	0.78 (0.59–1.02	0.76 (0.58–1.00)	225438.13	0
Female	0.71 (0.49–1.03)	0.73 (0.50–1.05)	199977.43	0
Region				
Asia	0.56 (0.37–0.85)	0.64 (0.44–0.95)	154637.71	0
Non-Asia	0.85 (0.65–1.11)	0.80 (0.61–1.04)	274414.41	0
Number of metastatic sites				
0–2	0.73 (0.56–0.94)	0.77 (0.59–0.99)	232964.07	0
≥3	0.84 (0.55–1.30)	0.67 (0.44–1.03)	214541.33	0
Previous gastrectomy				
No	0.81 (0.62–1.05)	0.84 (0.65–1.09)	566161.28	0
Yes	0.62 (0.41–0.94)	0.58 (0.38–0.87)	106015.93	0.20%
Primary site				
Stomach	0.69 (0.53–0.89)	0.67 (0.52–0.86)	163375.03	0
Gastro-oesophageal junction	1.02 (0.65–1.59)	1.07 (0.69–1.67)	—	—
Lauren classification				
Diffuse	0.76 (0.51–1.13)	0.77 (0.53–1.11)	234055.32	0
Intestinal	0.58 (0.38–0.89)	0.55 (0.36–0.85)	119418.99	0
Mixed or other	0.93 (0.60–1.43)	0.99 (0.64–1.54)	2792896.79	0
Country				
Japan	0.48 (0.23–1.01)	0.71 (0.41–1.25)	188331.92	0
Non-Japan	0.79 (0.63–1.00)	0.76 (0.60–0.96)	225670.02	0
China	0.50 (0.20–1.26)	0.91 (0.36–2.32)	198642.25	0
Non-China	0.75 (0.60–0.95)	0.74 (0.59–0.92)	207699.78	0
Race				
White	0.93 (0.68–1.27)	0.95 (0.70–1.29)	1051758.78	0
Asian	0.53 (0.35–0.79)	0.57 (0.39–0.83)	129440.25	0
Tobacco history				
Never	0.74 (0.54–1.01)	0.68 (0.49–0.93)	167176.02	0
Current	1.00 (0.48–2.09)	0.82 (0.40–1.69)	—	—
Former	0.71 (0.50–1.02)	0.81 (0.58–1.13)	273231.69	0

HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival.

TABLE 4 The cost and outcome results of the cost-effectiveness analysis.

Regimen	ZOL-FO	PLB-FO	Incremental
Total QALYs	1.64	1.23	0.41
Total costs, $	87746.35	11947.81	75798.54
ICER, $ Per QALY	—	—	185353.28

ICER, incremental cost-effectiveness ratio; PLB-FO, placebo plus mFOLFOX6; QALY, quality-adjusted life year; ZOL-FO, Zolbetuximab plus mFOLFOX6.

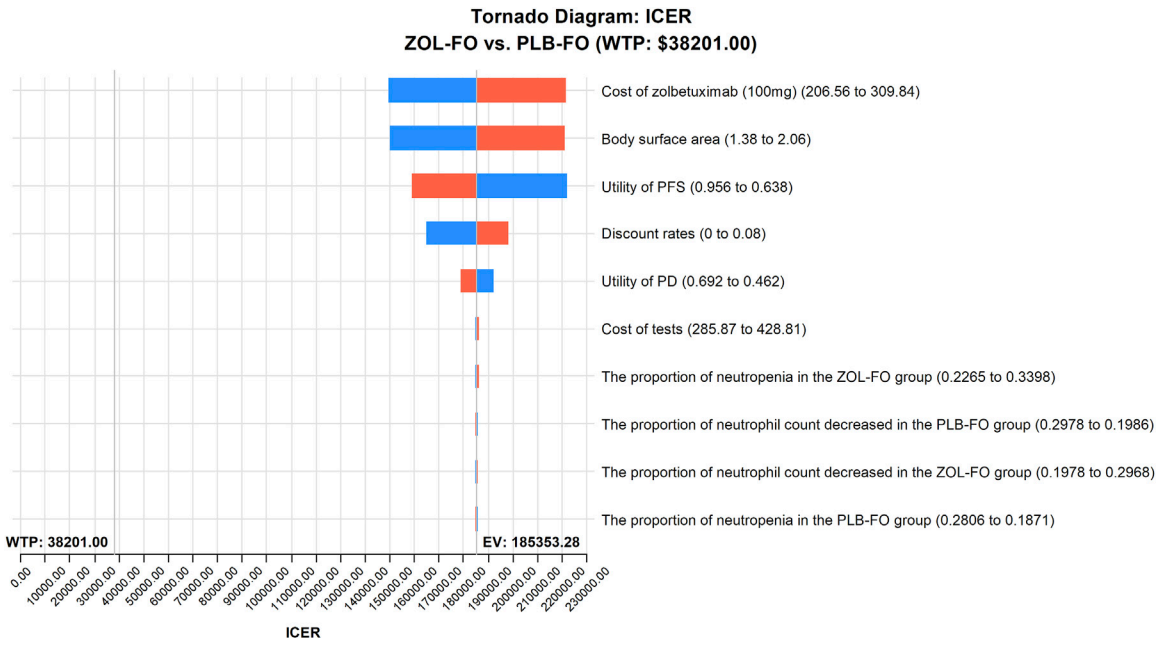

FIGURE 2
One-way sensitivity analyses of ZOL-FO in comparison with PLB-FO. ICER, incremental cost-effectiveness ratio; PD, progressive disease; PFS, progression-free survival; PLB-FO, placebo plus mFOLFOX6; ZOL-FO, zolbetuximab plus mFOLFOX6.

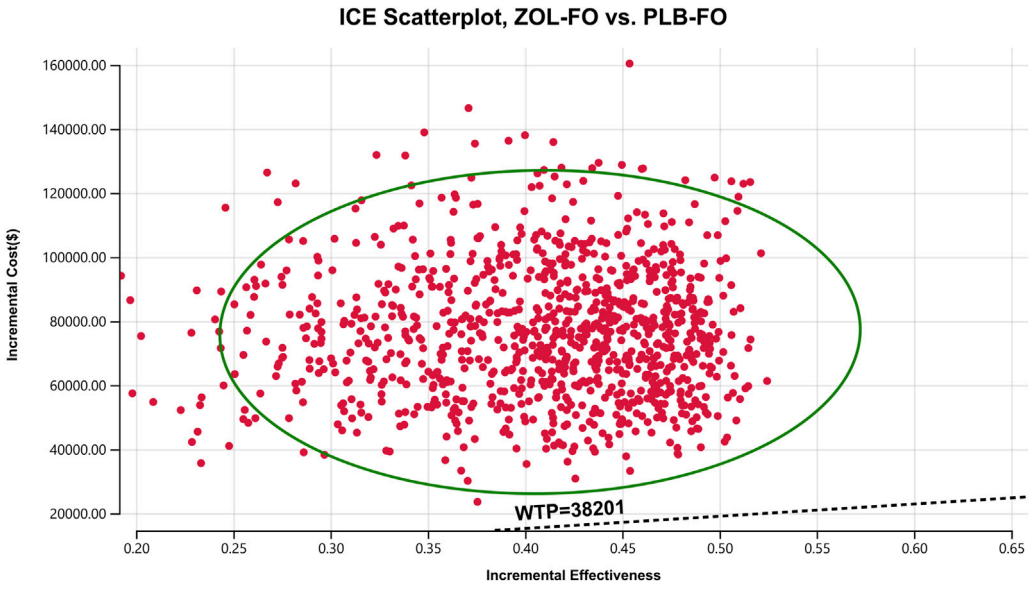

FIGURE 3
A probabilistic scatter plot of the ICER between the ZOL-FO group and the PLB-FO group. Each point means the ICER for 1 simulation. Ellipses are used to indicate 95% confidence intervals. Points that lie below the ICER threshold represent cost-effective simulations. ICER, incremental cost-effectiveness; PLB-FO, placebo plus mFOLFOX6; WTP, willingness-to-pay; ZOL-FO, zolbetuximab plus mFOLFOX6.

2023) CLDN18.2 is expressed in most G/GEJ adenocarcinoma cells (Shitara et al., 2023). The SPOTLIGHT trial evaluated the efficacy and safety of ZOL-FO as a first-line regimen for the treatment of CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma (Shitara et al., 2023). The trial found that ZOL-FO significantly prolonged OS [median OS, 18.23 vs 15.54 months, HR0.75(95%CI 0.60–0.94)] and PFS [median PFS, 10.61 vs 8.67 months, HR0.75(95%CI 0.60–0.94)] in

CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma compared with PLB-FO in safely and manageably, providing a new first-line treatment option for advanced G/GEJ adenocarcinoma. The results of the SPOTLIGHT trial are expected to drive the widespread use of zolbetuximab for treating CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma patients, leading to a significant increase in economic burden that will certainly become an important issue for healthcare decision-makers. Therefore, an economic evaluation of zolbetuximab is imperative.

To our knowledge, this study is the first to evaluate the cost-effectiveness of ZOL-FO as the first-line treatment option for patients with CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma, and its results will be instructive in China and other countries, which is the most important innovative point of this study. The results of this study show that ZOL-FO costs an additional $185,353.28 per additional QALY provided compared with PLB-FO, much higher than our predetermined WTP ($38,201/QALY). Thus, ZOL-FO for CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma is not cost-effective in China. Zolbetuximab costs much more than a placebo but does not provide a sufficient incremental survival benefit, which is the main reason it is not cost-effective. The results of the subgroup analysis also support that ZOL-FO is not a cost-effective treatment option. However, the results of this study should not be a reason to restrict the use of zolbetuximab, as it may result in a missed opportunity for beneficial treatment but should be considered as an economic reference for the country when negotiating drug prices (Yue et al., 2021). One-way sensitivity analysis also showed that zolbetuximab's cost was the most important factor affecting the model results. We, therefore, have made adjustments to the price of zolbetuximab to obtain different cost-effective results. ZOL-FO was cost-effective only when zolbetuximab (100 mg) was below $47.32.

Since 2018, the national health insurance administration has conducted several rounds of price negotiations with drug manufacturers for anti-cancer drugs, aiming to reduce the economic burden of cancer patients and society. The price of many anticancer drugs has been reduced by approximately 70% (Zhang Q. et al., 2021; Zhang et al., 2022). As of December 2022, China has approved the market launch of 16 immune checkpoint inhibitors (NMPA, 2023). In tertiary hospitals, the reimbursement rate for medical expenses of patients with medical insurance is approximately 70%, while primary healthcare institutions tend to offer an even higher reimbursement rate(Qin et al., 2023). These measures have significantly enhanced accessibility and affordability for patients. The results of this study are expected to provide the national health insurance administration with an economic reference for post-marketing price negotiations for zolbetuximab. We also recommend that manufacturers implement medication assistance programs after patients have completed a certain treatment cycle to enhance the accessibility of medications for patients.

Many antineoplastic drugs are considered uneconomical due to their small incremental survival benefit and high incremental cost for advanced GC (Shu et al., 2022). The results of Shu et al. (Shu et al., 2022) and Jiang et al. (Jiang et al., 2022) showed that nivolumab plus chemotherapy was not cost-effective as a first-line treatment for advanced gastric/gastroesophageal junction/esophageal adenocarcinoma compared with chemotherapy alone in China. The results of Li et al. (Li et al., 2020) suggest that for Chinese patients with advanced GC, second-line adjuvant therapy with ramucirumab combined with paclitaxel is unlikely to be cost-effective in a reasonable and expected range of drug costs. Chen et al. (Chen et al., 2017) suggest that apatinib is not cost-effective as third-line therapy for advanced GC in China. These are consistent with the results of our study.

Focusing solely on the cost-effectiveness evaluation of the treatment regimen from the perspective of China's healthcare system may lead to an underestimation of ZOL-FO's cost-effectiveness. As we know, China is classified as a developing country, and its *per capita* GDP is significantly lower compared to developed countries in Europe and America. In developed countries, the higher average income enables patients to more easily bear treatment costs, and medical insurance coverage is often more extensive. These factors may result in more widespread adoption of ZOL-FO in those countries, leading to a more positive impact on patients' treatment outcomes. Therefore, when evaluating the cost-effectiveness of ZOL-FO, it is essential to consider the economic conditions and disparities in healthcare systems among different countries. Furthermore, it is important to recognize the ethical issues of recommending expensive drugs to patients in oncology that have little to no clinical benefit. The occurrence of such situations is indeed regrettable and calls for further ethical and societal discussions to address them.

Our findings have other important advantages. First, ZOL-FO and PLB-FO were directly compared in the SPOTLIGHT trial, and our study used 4-year survival data from the recently published SPOTLIGHT trial. Second, 31% of the patients enrolled in the SPOTLIGHT trial were from Asia, so the results of the SPOTLIGHT trial can be extrapolated to a large extent to the Chinese population. Third, the economic outcomes of the 26 subgroups defined in the SPOTLIGHT trial were examined in this study, and physicians, patients, and policymakers may benefit from economic information about these subgroups.

However, our study has some limitations. First, due to practical limitations, we were unable to obtain long-term survival data, and a log-logistic survival model was used in this study to simulate data beyond the follow-up time frame, thus likely deviating from the real data. Second, we assumed that patients received the best supportive care at the time of disease progression, except for a subset treated with chemotherapy, targeted therapy, and immunotherapy, which may not accurately reflect the actual clinical situation. Third, only adverse events of grade 3 or higher with an incidence of >5% were included in the model. However, the results of the sensitivity analysis showed that changes in the incidence of adverse events did not significantly affect our results. Fourth, although we performed subgroup analyses, we should interpret this result with caution due to the small number of patients in the subgroup. Finally, the SPOTLIGHT trial did not provide data on quality of life, and the survival utility values in this study were derived from published literature in China, which may have led to bias in the model results but sensitivity analysis showed that our model was robust.

5 Conclusion

This study is the first to evaluate the cost-effectiveness of ZOL-FO from the perspective of the Chinese healthcare system using the results of recent clinical trials. Our results suggest ZOL-FO is not cost-effective as the first-line treatment for CLDN18.2-positive, HER2-negative advanced G/GEJ adenocarcinoma compared with PLB-FO.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material further inquiries can be directed to the corresponding author.

Author contributions

Study design and supervision: YH; data analysis and interpretation: RC; data collection: MY; manuscript writing: MY; final approval of the manuscript: All authors contributed to the article and approved the submitted version.

Funding

This study was supported in part by grants from the Natural Science Foundation of Fujian Province of China (Grant number: 2023J011910); Startup Fund for scientific research, Fujian Medical University (Grant number: 2022QH1203); Mindong Hospital Science Fund (Grant number: 2022YN005). This study was not supported by any pharmaceutical company.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1238009/full#supplementary-material

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frontiers | Frontiers in Immunology

TYPE Original Research
PUBLISHED 31 August 2023
DOI 10.3389/fimmu.2023.1223020

OPEN ACCESS

EDITED BY
Rob ter Heine,
Radboud University Medical Centre, Netherlands

REVIEWED BY
Dongzhe Hong,
Brigham and Women's Hospital and Harvard Medical School, United States
Shiwei Gong,
Huazhong University of Science and Technology, China

*CORRESPONDENCE
Yao Liu
swhliuyao@163.com

RECEIVED 18 May 2023
ACCEPTED 21 August 2023
PUBLISHED 31 August 2023

CITATION
Xiang G, Jiang T, Gan L, Wu Y, Zhang N, Xing H, Su H, Li Y, Peng D, Ni R and Liu Y (2023) Cost-effectiveness of serplulimab as first-line therapy for extensive-stage small cell lung cancer in China.
Front. Immunol. 14:1223020.
doi: 10.3389/fimmu.2023.1223020

Cost-effectiveness of serplulimab as first-line therapy for extensive-stage small cell lung cancer in China

Guiyuan Xiang, Tingting Jiang, Lanlan Gan, Yuanlin Wu, Ni Zhang, Haiyan Xing, Hui Su, Yanping Li, Dan Peng, Rui Ni and Yao Liu*

Department of Pharmacy, Daping Hospital, Army Medical University, Chongqing, China

Objective: The ASTRUM-005 trial demonstrated that adding serplulimab to chemotherapy significantly prolonged the survival of patients with extensive-stage small cell lung cancer (SCLC), but also increased the risk of adverse events. Given the high cost of serplulimab compared to chemotherapy, this study aimed to evaluate the cost-effectiveness of serplulimab plus chemotherapy as a first-line treatment for extensive-stage SCLC from the perspective of China's healthcare system.

Methods: A Markov model was developed to simulate the disease process of extensive-stage SCLC and estimate the health outcomes and direct medical costs of patients. Scenario analyses, univariate sensitivity analyses, and probabilistic sensitivity analyses were conducted to explore the impact of different parameters on model uncertainty. The primary model outcomes included costs, life-years (LYs), quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER).

Results: Compared to placebo plus chemotherapy, serplulimab plus chemotherapy resulted in an additional 0.25 life-years and 0.15 QALYs, but also increased costs by $26,402, resulting in an ICER of 179,161 USD/QALY. Sensitivity analysis showed that the ICER was most sensitive to the cost of serplulimab, and the probability that serplulimab was cost-effective when added to chemotherapy was only 0 at the willingness-to-pay threshold of 37,423 USD/QALY. Scenario analysis revealed that price discounts on serplulimab could increase its probability of being cost-effective.

Conclusion: Serplulimab plus chemotherapy is not a cost-effective strategy for first-line treatment of extensive-stage SCLC in China. Price discounts on serplulimab can enhance its cost-effectiveness.

KEYWORDS

cost-effectiveness, serplulimab, chemotherapy, extensive-stage small cell lung cancer, first-line treatment

1 Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with a staggering 2.2 million new cases and 1.8 million deaths annually (1). In China, lung cancer has the highest incidence and mortality rate among all cancers, with approximately 870,000 new cases and 770,000 deaths each year (2). Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two main histological classifications of lung cancer, with SCLC accounting for 10-15% of cases and having a 5-year survival rate of less than 7% (3). SCLC can be further divided into limited and extensive stages, with extensive-stage accounting for about 65% of new cases (4, 5). Platinum-based chemotherapy, particularly etoposide plus platinum (carboplatin/cisplatin), has been the standard first-line treatment for extensive-stage SCLC for the past three decades (6). However, in recent years, immunotherapy, including immune checkpoint inhibitors (ICIs), has emerged as a promising treatment option for SCLC. Several studies have shown that the addition of ICIs to chemotherapy for extensive-stage SCLC provides longer survival than chemotherapy alone, but some ICIs have been associated with increased incidence of serious adverse events (7–11).

Serplulimab, a fully humanized immunoglobulin G4 (IgG4) monoclonal antibody targeting the programmed cell death protein 1 (PD-1) receptor, was approved by the National Medical Products Administration (NMPA) in January 2023 for first-line treatment of extensive-stage SCLC based on the results of the ASTRUM-005 trial. ASTRUM-005 (ClinicalTrials.gov Identifier: NCT04063163) was a multicenter, randomized phase III trial compared serplulimab plus chemotherapy with placebo plus chemotherapy in the first-line treatment for patients with extensive-stage SCLC. The trial demonstrated that serplulimab plus chemotherapy prolonged median overall survival (OS) by 4.5 months (15.4 months vs. 10.9 months; Hazard ratio, 0.63 [95%CI, 0.49-0.82]) and median progression-free survival (PFS) by 1.4 months (5.7 months vs. 4.3 months; Hazard ratio, 0.48 [95%CI, 0.38-0.59]) compared with placebo plus chemotherapy. However, the serplulimab plus chemotherapy group had a higher incidence of grade 3 or higher treatment-related adverse events than the placebo group (33.2% vs. 27.6%) (12).

Despite the promising results of serplulimab, its cost-effectiveness needs to be evaluated. With the increasing number of newly marketed therapeutic drugs, clinical treatment must consider patients' affordability and health insurance funds' sustainability. Therefore, this study aims to evaluate the cost-effectiveness of serplulimab in combination with chemotherapy as first-line therapy for patients with extensive-stage SCLC from the perspective of China's healthcare system.

2 Methods

2.1 Model overview

This study adhered to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) guidelines for health economic evaluation (13). A Markov model was developed to estimate the cost and effectiveness of two treatment groups from the perspective of the healthcare system. The model consisted of four health states: progression-free survival (PFS), first disease progression (1st PD), second and subsequent disease progression, and death. Patients entered the model in the PFS state and then transitioned to other states (Figure 1A). The model cycle was 3 weeks, the time horizon was lifetime, i.e., the model was run until all patients died, yielding an actual time horizon of 7.44 years, and a half-cycle correction was applied in this model.

A total of 585 patients were randomly assigned to the serplulimab and placebo treatment groups in a 2:1 ratio upon entry into the model. The serplulimab and placebo groups received four 21-day cycles of serplulimab (4.5 mg/kg) and placebo treatment, respectively, while both groups received four 21-day cycles of etoposide (100mg/m2 on days 1, 2, and 3) and carboplatin (within the area under the concentration-time curve (AUC) of 5 mg/mL/min on day 1) treatment. The two groups then received serplulimab or placebo monotherapy until the first disease progression or death, respectively. Patients received subsequent treatment with second-line chemotherapy after the first disease progression until the second disease progression or death, and patients who could benefit from serplulimab or placebo in addition to second-line chemotherapy were also treated with serplulimab or placebo until the second disease progression or death, respectively. After the second disease progression, all patients received the best supportive care until death (Figure 1B). Patients in the model received second-line chemotherapy with irinotecan plus carboplatin or etoposide plus carboplatin in subsequent treatment. Based on data published in ASTRUM-005, we assumed that 55.23% of patients in the serplulimab group received serplulimab in subsequent treatment, and 50.23% of patients in the placebo group received placebo. Patients received carboplatin rather than cisplatin in subsequent treatment because of its lower toxicity than cisplatin.

2.2 Model survival and progression risk estimates

We extracted data from the published PFS and OS survival curves in the ASTRUM-005 trial using webplotdigitizer (Version 4.6, https://automeris.io/WebPlotDigitizer). We then generated pseudo-individual patient data according to Hoyle's algorithm (14). The survival curves were reconstructed using R software (Version 4.2.2, https://www.r-project.org/) and fitted to various survival distribution models, including Exponential, Weibull, Logistic, Log-logistic, and Log-normal models, to obtain the scale and shape parameters. The survival curves were extrapolated until all patients died. Based on the Akaike information criterion, Bayesian information criterion, and visual inspection, we selected the Weibull distribution model. We calculated the time-varying transition probabilities between each survival state using the survival function $S(t) = \exp(-\lambda t^{\gamma})$ ($\lambda > 0$; $\gamma > 0$). First, we calculated the PFS and OS probabilities at time t, denoted as P(t) and O(t), respectively. Then the probability of disease progression at t is calculated as $\text{Prob(FtP)} = [(P(t) - P(t + 1)]/P(t)$, and the

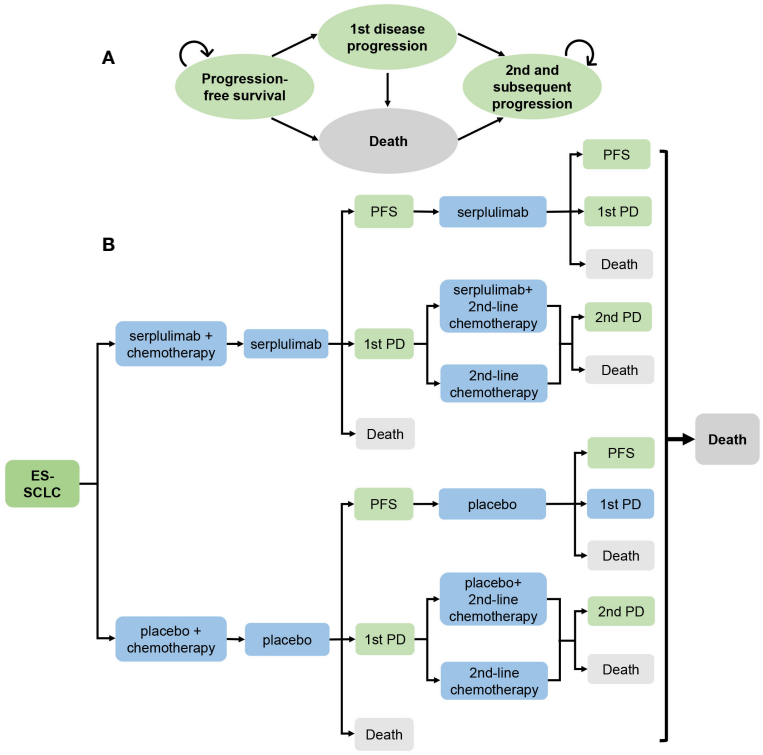

FIGURE 1
Model diagrams for analysis comparing serplulimab treatment vs placebo treatment in extensive-stage small cell lung cancer. **(A)** Simplified Markov Model. **(B)** Potential treatment pathways and decision tree. ES-SCLC, extensive-stage small cell lung cancer; PD, progressive disease; PFS, Progression-free survival.

probability of PD to death is Prob(PtD) = [(O(t) - O(t + 1)]/[(O(t) - P(t)]. The transition probabilities from PFS state to death state used a natural mortality rate in China in 2021 (15).

2.3 Cost estimates

From the healthcare system perspective, the model included direct medical costs such as drug costs, adverse events, best supportive care, follow-up, hospitalization, and laboratory test costs. Drug prices were obtained from the MENET database as the average of the bid prices for drug procurement across the provinces of China (16). Other costs were derived from published literature (17, 18), We adjusted costs for inflation to reflect 2022 price levels using the Chinese consumer price index (19). The exchange rate of USD 1 = CNY 6.87 in January 2023 was used in this study (20). The mean age of the patients in the model was 61.1 years, and the mean weight of the patients was assumed to be 65 kg, with a body surface area of 1.72 m^2 and a serum creatinine level of 1 mg/dL or 88.4 µmol/L. All doses were rounded to the nearest milligram. Adverse events of grade 3 and above with an incidence of 5% or higher were considered. The adverse events in both groups were decreased neutrophil count, decreased white blood cell count, decreased platelet count, and anemia in descending order incidence (Table 1).

2.4 Utility estimates

To measure effectiveness in this study, quality-adjusted life-years (QALYs) and life-years (LYs) were used. Since ASTRUM-005 did not report quality of life data, health utility values were obtained from published literature (18, 21). We used a utility of 0.673 in the PFS state and 0.473 in the first and subsequent disease progression states, and 0 in the death state for both treatment groups. The disutilities applied to adverse events were as follows: decreased neutrophil count (-0.2), decreased white blood cell count (-0.2), decreased platelet count (-0.19), and anemia (-0.073). In accordance with the recommendations of the Chinese Pharmacoeconomic Evaluation Guidelines (22), a discount rate of 5% per year was applied to both health outcomes and costs in both treatment groups in this study (Table 1).

2.5 Sensitivity analysis and scenario analysis

We conducted univariate sensitivity analysis and probabilistic sensitivity analysis to assess the robustness of the model. In the univariate sensitivity analysis, we varied cost, utility, and probability variables by ±20% of the baseline value, while the discount rate had a baseline value of 5% and was varied from 0-8%, as well as time

TABLE 1 Model inputs.

Parameter	Base case	Range		Distribution	Source
		Low	High		
Treatment cost per cycle ($)					
Serplulimab	2382.65	1906.12	2859.18	Gamma	16
Etoposide	362.36	289.89	434.83	Gamma	16
Irinotecan	312.03	249.62	374.44	Gamma	16
Carboplatin	55.41	44.33	66.49	Gamma	16
Best Supportive care	344.76	275.81	413.71	Gamma	17
Routine follow-up*	87.42	69.94	104.90	Gamma	17
Cost of managing adverse events ($)					
Anemia	533.61	426.89	640.33	Gamma	18
Decreased white blood cell count	489.30	391.44	587.16	Gamma	18
Decreased neutrophil count	88.42	70.73	106.10	Gamma	18
Decreased platelet count	1106.70	885.36	1328.04	Gamma	18
Health utility					
Progression-free survival	0.673	0.5384	0.8076	Beta	21
Progressive disease	0.473	0.3784	0.5676	Beta	21
Health disutility					
Anemia	0.073	0.0584	0.0876	Beta	18
Decreased white blood cell count	0.2	0.16	0.24	Beta	18
Decreased neutrophil count	0.2	0.16	0.24	Beta	21
Decreased platelet count	0.19	0.152	0.228	Beta	21
Discount rate	0.05	0	0.08	Fixed	–
Time horizon(years)	7.44	2.00	7.44	Fixed	–
Risk of AEs in serplulimab group					
Anemia	0.054	0.0432	0.0648	Beta	12
Decreased white blood cell count	0.085	0.0680	0.1020	Beta	12
Decreased neutrophil count	0.141	0.1128	0.1692	Beta	12
Decreased platelet count	0.062	0.0496	0.0744	Beta	12
Risk of AEs in placebo group					
Anemia	0.056	0.0448	0.0672	Beta	12
Decreased white blood cell count	0.087	0.0696	0.1044	Beta	12
Decreased neutrophil count	0.138	0.1104	0.1656	Beta	12
Decreased platelet count	0.082	0.0656	0.0984	Beta	12

AEs, adverse events; PD, progressive disease; PFS, Progression-free survival.
* The routine follow-up cost included outpatient physician visit, hospitalization, and laboratory tests.

horizon with a baseline value of 7.44 years, with a range of variation from 2.00-7.44 years. Additionally, we performed probabilistic sensitivity analysis using 1000 Monte Carlo simulations to explore the effect of simultaneous changes in multiple variables on the uncertainty of the model. The variables were assumed to vary in a specific distribution pattern, with cost variables assumed to follow a Gamma distribution, and utility and probability variables assumed to follow a Beta distribution, while the discount rate and time horizon remained fixed. The willingness-to-pay (WTP) threshold in the cost-effectiveness analysis was set at $37,423 per QALY, which is three times the per capita Gross Domestic Product (GDP) of China in 2022 (23). Furthermore, we evaluated the impact of different

price discount scenarios for serplulimab on ICER to provide a reference for health insurance reimbursement.

3 Results

3.1 Base-case results

The base-case results showed that the total cost of treatment per patient in the placebo group was $6789, while the cost in the serplulimab group was $33,191, which is $26,402 more than the placebo group (Table 2). In terms of health outcomes, the placebo and serplulimab treatments resulted in 1.25 and 1.51 life-years, respectively. After accounting for quality of life, each patient in the placebo and serplulimab groups gained 0.64 QALYs and 0.79 QALYs, respectively. The serplulimab group gained 0.26 life-years and 0.15 QALYs more than the placebo group per patient. Therefore, the incremental cost-effectiveness ratio (ICER) in the serplulimab group was $179,161/QALY or $102,535/LY compared to the placebo group. At the WTP threshold of 37,423 USD/QALY, the serplulimab treatment is not cost-effective.

3.2 Sensitivity analysis

The results of the univariate sensitivity analysis (Figure 2) indicated that the cost of serplulimab had the greatest impact on the ICER, with a range of $144,443-$213,879 per QALY when the cost of serplulimab varied by ±20%. The utility of the PFS state is second only to the cost of serplulimab in terms of its impact on ICER, and is followed by time horizon and the utility of PD state. Moreover, ICER values varied negatively with time horizon. Additionally, the risk of adverse events in the serplulimab and placebo groups also had a significant impact on the ICER. The discount rate had a significant effect on the ICER in the range of 0-8% change. However, regardless of which parameter varied individually within the established range, the ICER value remained above the $37,423 WTP threshold per QALY, indicating that the serplulimab group was consistently not cost-effective compared to the placebo group.

The probabilistic sensitivity analysis showed a mean incremental cost of $26,392, a mean incremental effectiveness of 0.15 QALYs, and an ICER of $178,927 per QALY for serplulimab versus placebo over 1000 Monte Carlo simulation iterations. The cost-effectiveness acceptability curve (Figure 3) shows that when the WTP threshold was set at $37,423 per QALY, the probability of serplulimab and placebo groups being cost-effective was 0 and 100%, respectively. The probability of serplulimab being cost-effective increased as the WTP increased, but the ICERs were above the WTP threshold of $37,423 per QALY for most combinations of variables.

3.3 Scenario analysis

We performed scenario analysis of different price discounts for serplulimab in the model. The results showed that when the cost of serplulimab decreased by 20% and 50%, the ICER was $144,443/QALY and $92,365/QALY, respectively. Probabilistic sensitivity analysis showed that the probability of cost-effectiveness of serplulimab was 0 in both cases. With other conditions remaining unchanged, the serplulimab group was cost-effective compared to the placebo group only if the price of serplulimab was reduced by 81.65% from the current price. At this price point, the total cost of treatment per patient in the serplulimab group was $12,304, and the ICER was $37,423 per QALY.

4 Discussion

The results of the phase III trial ASTRUM-005 revealed the significant efficacy of serplulimab in the treatment of small cell lung cancer, and serplulimab also became the first marketed PD-1 drug for the treatment of extensive-stage small cell lung cancer. We developed a four-state Markov model to evaluate the cost-effectiveness of serplulimab as a first-line treatment for extensive-stage SCLC, based on the results of the ASTRUM-005 trial. Our analysis suggested that the addition of serplulimab to chemotherapy resulted in an average survival benefit of 3.12 months per patient, equivalent to 0.15 QALYs gained. However, the cost of serplulimab

TABLE 2 Base case results.

Treatment	Total cost, $	LYs	QALYs	Incremental			ICER ($/QALY)
				Cost, $	LYs	QALYs	
Base case							
Placebo+ chemotherapy	6789	1.25	0.64	NA	NA	NA	NA
Serplulimab+ chemotherapy	33,191	1.51	0.79	26,402	0.26	0.15	179,161
Scenario analysis							
Placebo+ chemotherapy	6789	1.25	0.64	NA	NA	NA	NA
Serplulimab+ chemotherapy	12,304	1.51	0.79	5515	0.26	0.15	37,423

ICER, incremental cost-effectiveness ratio; LYs, life-years; NA, not applicable; QALYs, quality-adjusted life-years.

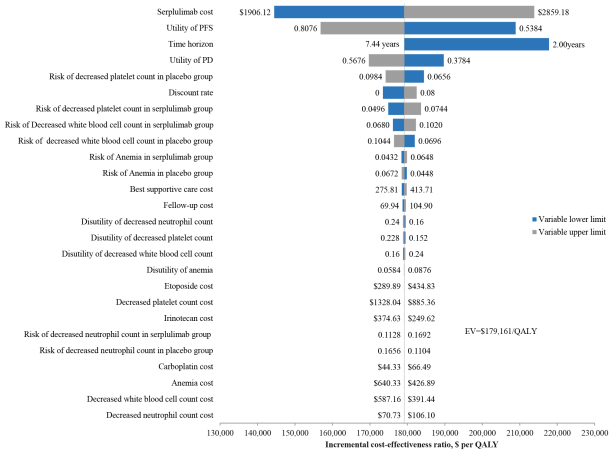

FIGURE 2
Univariate sensitivity analysis results for the base case analysis. QALY, quality-adjusted life-years.

was $26,402 per patient, resulting in an ICER of $179,161 per QALY. At the current WTP threshold of $37,423 per QALY in China, serplulimab plus chemotherapy is not considered a cost-effective treatment option.

The sensitivity analysis showed that the probability of adding serplulimab to chemotherapy was 0. The sensitivity analyses suggested that the addition of serplulimab to chemotherapy is less likely to be cost-effective. Since the price of serplulimab has the greatest impact on the model, we also conducted a scenario analysis to evaluate the impact of the cost of serplulimab on the model results. Our findings showed that the price of serplulimab would need to be reduced by at least 81.65% to make the immunotherapy regimen cost-effective at the base-case. Currently, the average price of serplulimab in China is 5588 Chinese yuan per 100 mg ($813.39/100 mg), implying that the price of serplulimab would need to drop to about 1205.31 Chinese yuan per 100 mg ($149.25/100 mg) for serplulimab to be considered cost-effective at the WTP threshold of three times per capita GDP of China. Currently, pharmacoeconomic evaluation plays an important role in the adjustments of the National Reimbursement Drug List (NRDL) of China. The Chinese government has conducted annual NRDL access negotiations since 2016, with the National Healthcare Security Administration (NHSA) as the main management department. In the process of access, firstly, expert review panel conducts a comprehensive evaluation on the safety, effectiveness, economy, innovation, suitability, and accessibility of drugs, and sets the payment price and negotiates base price of drugs based on the results of economic evaluation and budget impact analysis, and then negotiating expert panel conducts price negotiation with drug manufacturers on the basis of the base price to form the final payment price, with the final payment price not exceeding 115% of the base price (24). After a successful negotiation, drug prices would drop dramatically, NHSA will set the range of medical insurance payment indications and formulate a single medical insurance payment price. If the manufacturer of serplulimab succeed in negotiating with the NHSA in the future, serplulimab's cost-effectiveness would be greatly improved. In addition to the price of serplulimab, the health utility values of PFS and PD states also have a significant impact on the model, but there is currently a lack of research on the quality of life of patients with small cell lung cancer, and it is necessary to carry out relevant studies in the future to fill this gap to promote the economic evaluation of small cell lung cancer treatment drugs in China.

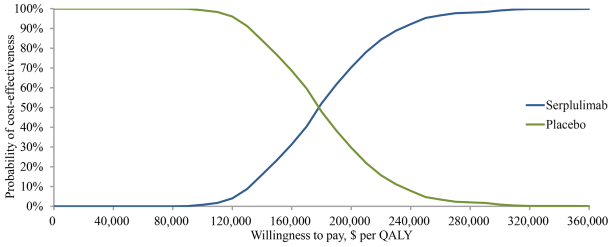

FIGURE 3
Cost-effectiveness acceptability curve for the base case analysis. QALY, quality-adjusted life-years.

The serplulimab regimen is not cost-effective at the current WTP threshold in China. Furthermore, when the results of this study are extrapolated to other high-income countries, such as the United States with a WTP threshold of $150,000 per QALY and the United Kingdom with a WTP threshold of £50,000 per QALY (25, 26), the combination of serplulimab and chemotherapy is still not considered cost-effective. However, if a higher WTP threshold is set for SCLC patients in the United States (27), this treatment regimen may become cost-effective.

Currently, Immunotherapeutic agents approved for extensive-stage SCLC in China include atezolizumab and durvalumab, in addition to serplulimab. Three studies have analyzed the cost-effectiveness of atezolizumab and durvalumab in combination with carboplatin and etoposide for the first-line treatment of extensive-stage SCLC from a Chinese payer perspective. The results showed that compared to chemotherapy regimens, the ICERs for atezolizumab plus chemotherapy were $489,013 per QALY, and for durvalumab plus chemotherapy, they were $192,591 per QALY and $230,142.9 per QALY (28–30). Therefore, neither combination regimen was cost-effective compared to chemotherapy regimens. Although the ICER for serplulimab plus chemotherapy in this study was lower than those for atezolizumab and durvalumab, it was still well above the WTP threshold. Reducing the price of serplulimab remains a potential solution to make it cost-effective. Meanwhile, risk-sharing agreements are still a worthwhile payment method for China's health insurance administration. Serplulimab was only recently approved for the first-line treatment of extensive-stage SCLC in 2023, and further evaluation of its economics based on real-world data generated in clinical use is still needed to inform clinical and health insurance reimbursement decisions. While value-based pricing has been successfully applied in China, the increase in indications for serplulimab or other ICIs, and the varying clinical value of different indications, make multi-

indication pricing another promising approach. Therefore, conducting an economic evaluation of multi-indications in the future is necessary to provide a reference for the authorities.

In terms of clinical treatment decision-making for extensive-stage SCLC, we suggest that clinicians need to consider not only the patient's disease status, but also the patient's ability and willingness to pay when developing a treatment plan, and prioritize the selection of medicines that have been included in the NRDL. Standard chemotherapy may be preferred for patients with poor ability to pay but who tolerate platinum-based agents well. At the same time, China's current economic development is highly uneven, and the level of economic development among provinces is quite different. Different regions should combine the local economic development level when referring to the results of this study. For example, the per capita regional GDP of Beijing and Shanghai in 2022 (27,729 USD in Beijing and 26,252 USD in Shanghai) is more than twice the national per capita GDP, the probability of serplulimab being cost-effective in this location is increased (31, 32). In addition, it is recommended that the manufacturer of serplulimab develop a suitable Patient Assistance Program (PAP) to provide pharmaceutical assistance to patients who are impoverished due to illness or who are enduring catastrophic health expenditures, in order to improve the accessibility of serplulimab.

There are still several limitations in our study. ASTRUM-005 reported a large number of second-line treatment regimens during the maintenance phase, which led us to simplify the model by assuming that the second-line chemotherapy regimen is only irinotecan plus carboplatin or etoposide plus carboplatin. We did not consider targeted therapies, herbal or traditional Chinese medicine, or other immunotherapies except serplulimab and placebo, which may have caused ICER bias. Additionally, since ASTRUM-005 has no published quality of life measurement data, and there is no study on the health utility of SCLC in China, the health state utility values in this study were mainly derived from the study of health state utilities of NSCLC by Nafees B et al. However, the malignancy of SCLC is higher than that of NSCLC, and its actual utility may be lower than that of NSCLC, resulting in a higher ICER.

5 Conclusion

In conclusion, this study found that serplulimab plus chemotherapy is not a cost-effective treatment strategy for extensive-stage SCLC in China at the current WTP threshold. Reducing the price of serplulimab remains a potential solution to make it cost-effective. Further evaluation of its economics based on real-world data generated in clinical use is still needed to inform clinical and health insurance reimbursement decisions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

YLiu and GX were responsible for the conception and design of the study. GX contributed to the model building and drafted the manuscript. YLiu supervised the project. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Chongqing Clinical Pharmacy Key Specialties Construction Project [Grant 425Z41]; the Joint project of Chongqing Health Commission and Science and Technology Bureau [Grant 2023ZDXM032].

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 31 August 2023
DOI 10.3389/fphar.2023.1215431

OPEN ACCESS

EDITED BY
Atse Huisman,
Health Insurers Netherlands, Netherlands

REVIEWED BY
Sibren Van Den Berg,
Academic Medical Center, Netherlands
Noraly Stam,
National Healthcare Institute (ZIN), Netherlands

*CORRESPONDENCE
Antonio Vallano,
avallano@catsalut.cat

RECEIVED 01 May 2023
ACCEPTED 21 August 2023
PUBLISHED 31 August 2023

CITATION
Vallano A, Pontes C and Agustí A (2023), The challenges of access to innovative medicines with limited evidence in the European Union.
Front. Pharmacol. 14:1215431.
doi: 10.3389/fphar.2023.1215431

The challenges of access to innovative medicines with limited evidence in the European Union

Antonio Vallano[1,2,3]*, Caridad Pontes[1,2,4] and Antònia Agustí[2,5]

[1]Medicines Department, Catalan Healthcare Service, Barcelona, Spain, [2]Department of Pharmacology, Therapeutics and Toxicology, Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Healthcare Management of Hospitals, Catalan Institute of Health, Barcelona, Spain, [4]Digitalization for the Sustainability of the Healthcare System DS3-IDIBEL, L'Hospitalet de Llobregat, Spain, [5]Clinical Pharmacology Service, Vall d'Hebron University Hospital, Barcelona, Spain

The European Medicines Agency (EMA) fosters access to innovative medicines through accelerated procedures and flexibility in the authorization requirements for diseases with unmet medical needs, such as many rare diseases as well as oncological diseases. However, the resulting increase of medicines being marketed with conditional authorizations and in exceptional circumstances has lead to higher clinical uncertainty about their efficacy and safety than when the standard authorizations are applied. This uncertainty has significant implications for clinical practice and the negotiation of pricing and reimbursement, particularly as high prices are based on assumptions of high value, supported by regulatory prioritization. The burden of clinical development is often shifted towards public healthcare systems, resulting in increased spending budgets and opportunity costs. Effective management of uncertainty, through appropriate testing and evaluation, and fair reflection of costs and risks in prices, is crucial. However, it is important not to sacrifice essential elements of evidence-based healthcare for the sake of access to new treatments. Balancing sensitive and rational access to new treatments, ensuring their safety, efficacy, and affordability to healthcare systems requires thoughtful decision-making. Ultimately, a responsible approach to timely access to innovative medicines that balances the needs of patients with healthcare systems' concerns is necessary. This approach emphasizes the importance of evidence-based decision-making and fair pricing and reimbursement.

KEYWORDS

drug approval, drug costs, orphan drug, antineoplastic agents, European Union

1 Introduction

In recent years, there have been significant technological advances in biomedical research that have been quickly translated into clinical practice (Zeggini et al., 2019; Tsimberidou et al., 2020). The pharmaceutical industry is shifting its focus from traditional research and development programs targeting common diseases to a new approach of discovering treatments for rare and hard-to-treat illnesses with unmet medical needs (Attwood et al., 2018). However, these advances also come with a significant increase in healthcare costs (Keehan et al., 2015).

The European Medicines Agency (EMA) plays a significant role in evaluating pharmacological innovations and issuing opinion for their commercialization in the European Union (EU) countries (European Medicines Agency, 2020a). The European

Commission then ultimately authorizes the marketing of these medicines in the EU (EUR-Lex, 2004). However, the decision on the pricing and financing of these medications with public funds is a competence of the individual member states (Antoñanzas et al., 2005; Löblová, 2021; Vončina et al., 2021). Finally, regional or local governments, health centers, and healthcare professionals are responsible for deciding which medications to prioritize for certain patients or circumstances in a domestic context.

There is a demand that the process of access to innovative medicines should be faster, and patients should have timely access to new and innovative medicines (Annemans et al., 2011; Baird et al., 2014; Panteli and Edwards, 2018). For life-threatening or debilitating diseases that have limited or no treatment options, access to new drugs can provide relief and improve the quantity and quality of life for existing patients with ominous prognosis. However, many healthcare stakeholders claim that numerous patients with life-threatening or debilitating diseases still do not have access to new and innovative medicines (Baird, et al., 2014; Panteli and Edwards, 2018; Horgan, et al., 2022).

The EMA has acknowledged the existence of unmet medical needs and have established laws and regulations aimed at expediting the development and approval of drugs to address these specific diseases (EUR-Lex, 2004). A group of experts with representatives from the rare disease community, researchers, patient advocates, investors, and pharmaceutical companies has proposed several measures to promote rare disease medicine, including a faster regulatory process (Aartsma-Rus et al., 2021). However, when it comes to regulatory processes enabling quick access to new medicines, it entails accepting a higher level of uncertainty during the approval stage. This has sparked ongoing discussions regarding the most suitable trade-off between speed and the evidence required for the development of new medicines.

In this article we will delves into the complex subject of medications authorized with limited clinical evidence. There are several reasons for granting access to medicines with limited evidence (Table 1). We aim to examine various scenarios encountered in clinical research, including trials conducted without a control group, studies involving a restricted number of participants and limited available information, utilization of surrogate endpoints, accelerated authorizations based on promising initial results pending confirmation from more robust data, as well as conditional authorizations granted under exceptional circumstances. Furthermore, our attention is directed towards the intricate challenges that arise during the decision-making process concerning the funding of these medications. This is particularly noteworthy due to the limited clinical evidence and frequently elevated costs associated with such treatments. Therefore, a thorough evaluation of resource allocation and an assessment of the value and cost-effectiveness associated with these interventions are needed.

TABLE 1 Justification for access to medicines with limited evidence.

• Diseases with limited treatment options
• Urgency of treatment in life-threatening or debilitating diseases
• Opportunity costs of patients at high unmet medical needs
• Difficulties and high costs of research in small populations at high need
• Fast dissemination of early evidences of potentially breakthrough therapies
• Regulatory recognition of unmet medical needs
• Social demand of access to innovation

2 Actions to accelerate regulatory access to innovative medicines

Medicine regulation by the EMA aims to ensure that only medicines with a favorable balance of benefits and risks are authorized for marketing. This requires the assessment of three criteria: quality, efficacy, and safety (European Medicines Agency, 2020a). However, conducting the necessary studies to evaluate these criteria can be costly and time-consuming. Incentives have been put in place to encourage research and innovation in areas with high unmet medical need, which can result in a flexibility of regulatory requirements and shortened assessment timelines to avoid delays in access to treatment, especially for serious and urgent illnesses. Therefore, in some cases the regulation procedure offers incentives and is faster and more flexible.

The European Union incentivizes the development of medicines that are intended to treat small patient populations, assuming that the development of these types of medicines may not be financially viable under normal market conditions. The EMA's Committee for Orphan Medicinal Products (COMP) grants orphan designation to medicines that treat life-threatening diseases with a low prevalence in the EU and offer significant benefits over existing treatments or fill a gap where no satisfactory treatments exist. Orphan drug designation recognizes that the drug is addressing a relevant unmet need, and offers several incentives, including reduced or waived fees, protocol assistance (scientific advice specific to orphan drugs), and 10 years market exclusivity in the EU (EUR-Lex, 2000; European Medicines Agency, 2022a). Orphan medicinal products (OMP) are qualified as such after receiving a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) (European Medicines Agency, 2022a).

Accelerated review processes have been developed to reduce the time required by the EMA to review a marketing authorization application for medicines that are considered important therapeutic innovations and are of great public health interest. This expedited review process reduces the review procedure time from 210 days to 150 days, if the applicant provides good cause for an expedited review (European Medicines Agency, 2021a).

The PRIME (PRIority MEdicines) program is an initiative developed by the EMA to improve and accelerate the evaluation and approval process of medicinal products aimed to treat serious and life-threatening conditions with unmet medical needs. The program offers ongoing assistance for the advancement of qualified medications, which have been chosen based on their potential to provide substantial therapeutic benefits compared to current treatments or to benefit patients who lack treatment options altogether. The primary objective is to streamline the medicine development process and expedite access to these innovative treatments (European Medicines Agency, 2023a). The PRIME program provides early and proactive support to medicine developers to generate robust data on the benefits and risks of a

TABLE 2 Medicines with positive opinions from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) from 2015 to 2022.

	2015 (n = 92)	2016 (n = 81)	2017 (n = 92)	2018 (n = 84)	2019 (n = 66)	2020 (n = 97)	2021 (n = 92)	2022 (n = 89)	Total (n = 693)
News active ingredients	39	27	35	42	30	39	54	41	307
Orphan medicines	18	16	19	21	7	22	19	21	143
ATMPs	1	2	2	3	1	3	2	6	20
Accelerated procedures of authorization	5	7	7	4	3	5	3	5	39
PRIME program				3	3	8	6	8	28
Type of marketing authorization									
Standard	87	72	87	80	57	79	75	75	612
Conditional	3	8	3	1	8	13	13	9	58
Exceptional circumstances	3	1	2	3	1	5	4	5	24

ATMPs, Advanced therapy medicinal products.

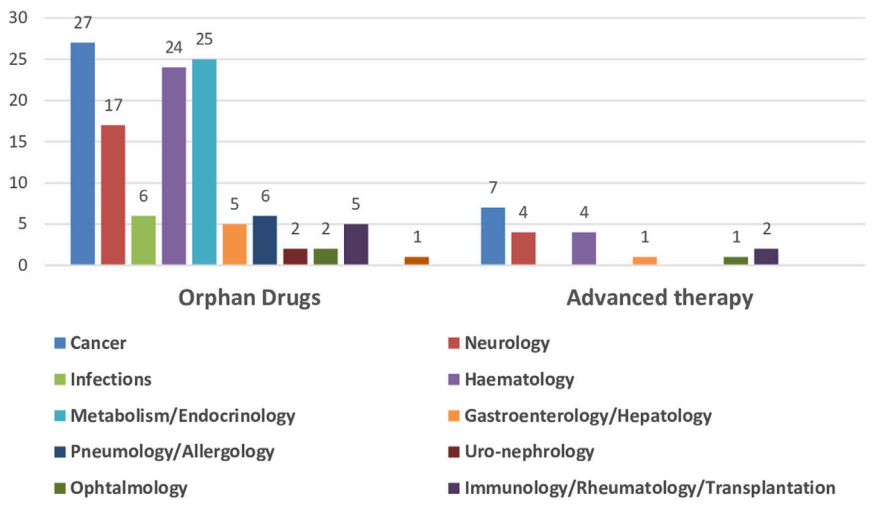

FIGURE 1
Number of orphan drugs and advanced therapies authorized by CHMP to treat diseases in different therapeutic areas, 2016–2021.

drug, and to accelerate the assessment of applications for medicine approvals through early interaction and dialogue with regulators. PRIME allows applicants to receive confirmation during the clinical development phase on whether their drug may be eligible for accelerated assessment (European Medicines Agency, 2023a).

A comprehensive review of the PRIME scheme's experience since inception and up to June 2021 has been carried out (European Medicines Agency, 2018a; European Medicines Agency, 2022b). The monthly average of PRIME applications in the period was 6.1, with a total of 384 requests of which 25% (N = 95) being granted. Oncology products made up the majority of applications (29%), while advanced therapy medicinal products (ATMPs) had the highest success rate (46%). Orphan-designated products made up 42% of PRIME eligibility applications, and 56% of PRIME products granted eligibility had an orphan designation. Medicines with a PRIME designation more often have conditional authorizations than medicines without this designation (European Medicines Agency, 2022b).

The impact of the regulatory procedures mentioned above has been a progressive increase in the authorization of medicines with orphan and advanced therapies designations (European Commission, 2020; Technopolis Group, 2020) (Table 2). In addition, conditional marketing authorizations and marketing authorizations under exceptional circumstances have also increased, as well as, PRIME designation and accelerated authorization procedures (Table 2) (European Medicines Agency, 2016; European Medicines Agency, 2017; European Medicines Agency, 2018b; European Medicines Agency, 2019; European Medicines Agency, 2020b; European Medicines Agency, 2021b; European Medicines Agency, 2022c; European Medicines Agency, 2023b). The number of orphan drugs and advanced therapies with positive opinion of CHMP to treat diseases in different Therapeutic

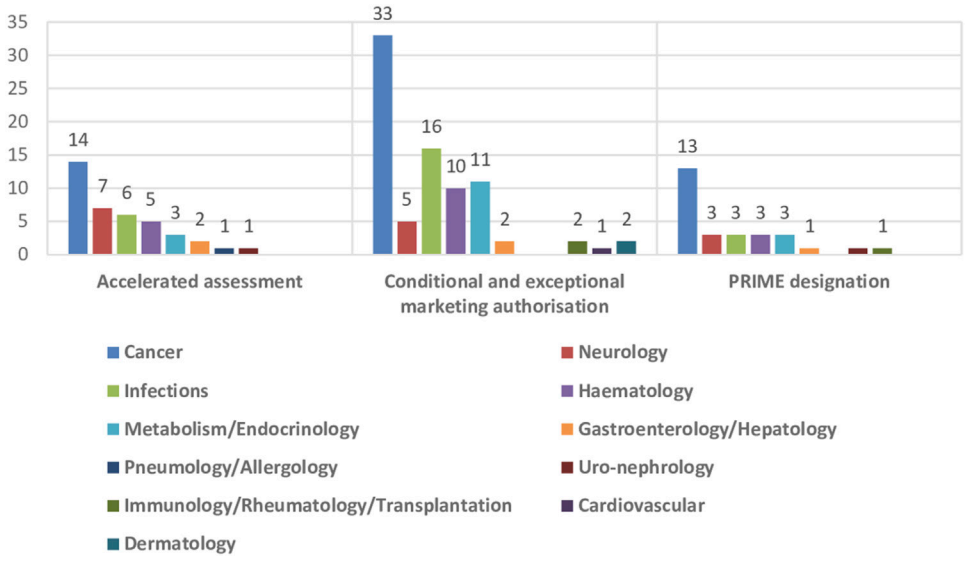

FIGURE 2
Number of accelerated assessments, conditional and exceptional marketing authorisations, and PRIME designations for medicines with positive opinion from the CHMP for treating diseases in different therapeutic areas, 2015–2021.

Areas from 2016 to 2021 is shown in Figure 1. The number of accelerated assessments, conditional and exceptional marketing authorizations, and PRIME designations for medicines with positive opinion from the CHMP for treating diseases in different therapeutic areas from 2015–2021 is shown in Figure 2. Oncology is the therapeutic area with more orphan drugs, advanced therapies, accelerated assessments, conditional and exceptional marketing authorizations, and PRIME designations.

It must be emphasized that currently the European Commission is proposing a review of European Union pharmaceutical legislation, consisting of a new Directive and a Regulation to simplify and replace the previous legislation. The new legislation will promote innovation in the development of new medicines by speeding up the authorization process with simplified procedures, offering tailored scientific support and advice for innovative products, and providing special incentives for rare diseases. The reform aims to provide all patients in the EU with timely and equitable access to safe and effective medicines, and offering incentives for the development of innovative medicines addressing unmet medical needs (European Commission, 2023).

3 Uncertainty and consequences of access to innovative medicines with limited evidence

3.1 Uncertainty of benefit at authorization and during the post-marketing period

However, rapid access to new medicines from the regulatory side means that in most cases, more uncertainty is accepted at the time of approval, and there is still debate about the optimal balance between speed and evidence for developing new medicines. A review of oncology medicines approved by the EMA from 2015 to 2020 found that most medicines were approved for marketing based on surrogate outcomes, without evidence of improved overall survival (OS) or quality of life benefits (Falcone et al., 2022).

Moreover, there is concern on the actual magnitude and relevance of the clinical benefit, and balance with added toxicities of newly authorized products. An analysis of OS data of new cancer medicines approved by the US Food and Drug Administration (FDA) and the EMA between 2003 and 2013 found that only 43% of the drugs showed an increase of at least 3 months, 11% showed less than 3 months, and 30% showed no improvement in OS. The average increase in OS was of 3.4 months, and the majority of the new cancer medicines were also associated with increased toxicity (Vega et al., 2017). The analysis of 38 cancer medicines for solid tumors approved by the EMA between 2011 and 2016 found that the results of 89% out of the 70 supporting pivotal trials did not meet the threshold of clinical relevance on the ESMO-MCBS scale, suggesting that the clinical benefit of these drugs may be questionable (Grössmann et al., 2017).

To note, clinical trials are increasingly adopting methodologies that allow early interruption led by interim analysis, if supporting positive results. However, early trial interruption may led to overestimation of effects, especially if decisions are not taken blinded to treatment groups, or are based on uncontrolled designs (Montori et al., 2005; Bassler et al., 2010). Often, sponsors do not adequately report on the decision to stop, and large treatment effects are show that are unlikely to be confirmed later on, especially when the number of events is small. A study of clinical trials that were stopped early for benefit found that these trials typically included 63% of the planned sample size and were stopped after a median of 13 months of follow-up, with an intermediate interim analysis and a median of 66 patients. The trials did not report at least one of the following characteristics: planned sample size, interim analysis, whether a stopping rule informed the decision, or an adjusted analysis accounting for

interim follow-up and truncation. Trials with fewer events produced larger treatment effects, thus suggesting that the results of these early-stopping trials may be frail and potentially biased, and should be regarded with high caution (Montori et al., 2005; Walter et al., 2019; Liu and Garrison, 2022).

On top of that, the evidence on new drugs that are addressed to small populations, such as OMPs and ATPMs, may also be flawed by the use of weak methodological approaches. A review of the European Public Assessment Reports (EPARs) of 125 OMPs approved by the EMA between 1999 and 2014 found that one third of the trials did not include a control arm, one third did not use randomization, half of the trials were open-label, and 75% used intermediate or surrogate outcomes as the primary endpoint. The size of the population exposed at the time of OMPs approval was smaller than needed to classify adverse reactions as clinically relevant, and 10% of the OMPs were approved despite the results of the pivotal trials being negative (Pontes et al., 2018). This suggests that the regulatory evidence supporting OMPs approval had significant uncertainties, including weak protection against bias, substantial use of inappropriate study designs, reliance on intermediate outcomes, lack of prioritization, and insufficient safety data to accurately quantify risks.

Currently, some ATMPs have already been commercialized. A review of pivotal clinical trials (CTs) supporting the approval of ATMPs by EMA found that their approval was mainly based on small CTs, single-arm, no control group, compared to historical controls, and using surrogate outcomes as the primary endpoint (Iglesias-Lopez et al., 2021a). Additionally, in an analysis of the ATMPs approved by EMA and FDA, many of ATMPs had an orphan drug designation, expedited program designation, quick decision on marketing authorization, and non-standard marketing authorization (Iglesias-Lopez et al., 2021b). There are various health and economic adverse consequences with the marketing of medications with limited clinical evidence. Since these medicines are still in the early stages of development, the safety and efficacy of the medicine may not be well established, and thus one of the primary risks of their market access is the lack of sufficiently robust safety and efficacy data for these medicines. This may risk serious side effects and lack of meaningful benefit to the patient. While additional information will be accrued on the efficacy and safety of the medicines in the early marketing period, clinical trials may become unfeasible for recruitment once the product is available, and observational data often does not provide further relevant and robust evidence, so that clinical uncertainty may not be resolved.

From 2009 to 2013, the EMA approved the use of 48 anticancer medicines for 68 indications. In 12% of the indications pivot trials had a unique arm study, in 35%, OS data were not available, and in those that were available, the median overall survival benefit was 2.7 months (range 1–5.8 months). Quality of life data only were available in 10% of cases. In post-marketing follow-up data only 3 of 44 indications that initially had no overall survival data showed an overall survival gain or benefit in post-marketing outcomes. Median follow-up after authorization was 5.4 years (range, 3.3–8.1 years). Of the 23 drugs with an ESMO score, 12 (52%) had a score indicating non-significant improvement. For about half (33; 49%) the post-marketing benefit was still uncertain. Therefore, about 50% of medicines authorized for licensed oncology indications remained uncertain after an average of 5.4 years after approval (Davis et al., 2017).

Conditional marketing authorizations should be reversible if benefit assumptions are not met, but in clinical practice, they barely are. For instance, in the case of ataluren, the conditional marketing authorization by EMA was issued without conclusive evidence on efficacy in pivotal clinical trials, but based on contextual reasons and a reasonably safety profile (Haas et al., 2015). Subsequent clinical trials failed to conclude efficacy, but the medicine is still commercialised with annual treatment costs over €200,000 per year (McDonald et al., 2017). Olaratumab received an accelerated and conditional approval based on exceptional efficacy in a single phase 2 trial, awaiting the results of a phase III clinical trial, and rapidly taken up into clinical practice. However, the phase 3 trial failed to conclude efficacy and was withdrawn by the company, although thousands of patients had already been treated in the EU with a cost greater than thirty million euros (Pontes et al., 2020).

3.2 Uncertainty in pricing and reimbursement process

Pricing and reimbursement (P&R) decisions for innovative medicines are a complex and challenging task for health systems, as they balance the need to provide access to new treatments with the need to control costs and ensure long-term sustainability. The P&R process involves evaluation of the clinical and economic value of new medicines, considering factors such as clinical efficacy, safety, cost-effectiveness, and budget impact. It also requires taking into account the perspectives of various stakeholders, including patients, pharmaceutical companies, healthcare providers, payers, and policymakers. When there is a great unmet medical need and no therapeutic alternatives available, the decision making process becomes even more challenging. The perception of high value for accelerated, conditional, or exceptional authorizations can lead to high expectations, associated with high prices, from agents of interest and social pressure for hard bargaining. In these cases, there are no competitors, and therefore no comparative data to go on.

Companies are unwilling to set low prices for their products, tend to overestimate the cost-effectiveness of their therapies, and claim theoretical prices that are expected to return costs of manufacturing, R&D investments and reward value of innovation (Saluja et al., 2021). However, R&D costs are not transparent and traceable enough, there are no clear rules on how to consider the amount of effort done up to the P&R decision (especially in early approvals) nor on how different countries must bear and share the burden of such investment returns. Consequently, a variation in pricing, funding decisions, and time to reimbursement for innovative medicines, which encompasses OMPs, ATPMs, and anticancer drugs, across European countries has been described (Martinalbo et al., 2016; Szegedi et al., 2018; Cufer et al., 2020; Iglesias-Lopez et al., 2022; Post et al., 2023). This fuels disparities in patient access to these medicines throughout the diverse European countries. It is worth highlighting that indications for use of the new innovative medicines, such as OMPs, trend to be progressively smaller, while their relative spending has steppedly increased over 20 years across European countries, and the cost per patient

is progressively higher (Mestre-Ferrandiz et al., 2019). Medicines with costs per patient exceeding 1 million euros have recently been marketed (Nuijten, 2022) The proliferation of very expensive drugs has sparked debate about their sustainability and affordability (Kang et al., 2021).

4 Discussion

Access to innovative medicines for patients with rare diseases and unmet medical needs is crucial. However, the uncertainties inherent in developing those medicines with a limited evidence pose significant challenges to traditional health technology assessment, and P&R processes.

Firstly and foremost, it is vital to enhance the scientific evidence of those medications. Classic confirmatory clinical trial designs with randomization and control groups, with the best available treatment option, should be the best option, as longas it is feasible (Hulley et al., 2013). This approach ensures rigorous evaluation of treatment efficacy and safety. In addition, it is important to evaluate variables that are clinically relevant, rather than surrogate variables, and demonstrate benefits that are of clinical relevance. This means focusing on outcomes that directly impact patients' health and wellbeing. Broadening eligibility criteria and avoiding unnecessary exclusions can help to increase the number of included patients in clinical trials, particularly when addressing rare diseases. However, within the realm of rare diseases, where patient populations tend to exhibit a notable heterogeneity, the mere expansion of participant numbers could potentially complicate the interpretation of trial outcomes. This complication might give rise to challenges in pinpointing the specific subgroups that derive benefits from treatments, owing to the inadvertent inclusion of patients with disparate phenotypes. If the traditional design is not feasible, alternative designs such as adaptive designs, and trial designs that aim to gather the maximum amount of useful data from a reduced number of patients could be considered (Pallmann et al., 2018; Subbiah, 2023). Post-marketing real world data has been put forth as a potential surrogate in the absence of good evidence from clinical trials (Swift et al., 2018). However, pragmatic post-marketing research produces a less robust evidence than pre-marketing experimental studies (Makady et al., 2019a).

Secondly, payers may have doubts about the effectiveness, safety, and therapeutic value of a treatment that has not been fully confirmed because they need accurate information to decide P&R of these innovative medicines (Simoens, 2011). There is a concern that payers and society may be burdened with the costs of unproven yet expensive treatments. Healthcare stakeholders should take a comprehensive approach to assess decision-making on access to innovative medicines with limited evidence. This may include restrictive access decisions for conditionally approved products through requesting robust evidence based on well-designed clinical trials able to evaluate both relevant clinical and non-clinical outcomes, in order to ensure guarantees of efficacy and safety of those products and economic sustainability at the population level (Lau and Dranitsaris, 2022).

The regulatory approval process has undergone meticulous review and adaptation to facilitate access of innovative medicines. Similarly, there seems to be a need to revisit the P&R system, through a transparent and evidence-based approach, as well as an effective price regulation, that is able to manage the greater amount of uncertainty resulting from regulatory measures to accelerate access of innovation (World Health Organization Regional office for Europe, 2018).

Fixing a price on a population level, as well as a spending cap per patient, in an uncertain setting should not result in premium prices based on expectations, but on prices that are proportional to its value at the time of P&R, considering the magnitude of benefit but also the strength and different levels of the evidence supporting it. If the evidence for a medicine's efficacy and safety is weak, the price should also be lower, regardless of other factors, at least until the expectations can be robustly confirmed.

A strategy often applied to manage clinical uncertainty of expensive medicines aimed to small populations are risk-sharing agreements or managed access agreements (MAA) (Bouvy et al., 2018; Dabbous et al., 2020). Thus, when weak clinical evidence, and value and economic uncertainties derive from a large budget impact, an option is measuring outcomes in clinical practice, and linking actual effectiveness to sharing of financial risks. The collection of additional data after conditional authorization aids to confirm that the benefits outweigh the risks, and to ensure that the medicine is able to meet the needs of the population. In this way, risk-sharing arrangements may balance the need to provide rapid access to potentially beneficial medicines with the need to circumscribe uncertainty, obtaining the best value for money and ensuring affordability (Dabbous et al., 2020). Nevertheless, MAA that require collecting additional data by stakeholders (companies and healthcare professionals) may result in biases in support of access, led by conflicts of financial and clinical interests, respectively.

Curiously, the introduction of a medical product to the market with substantial uncertainty, does not inherently lead to the implementation of performance-based agreements. Between 2006 and 2016, managed entry agreements based on clinical outcomes were not commonly used for products that had a conditional marketing authorization or those that were authorized under exceptional circumstances. Of the 48 products that received marketing authorization under exceptional or conditional circumstances in recent years, only a few were found to have managed entry agreements involving the collection of additional data. The complexity of collecting outcomes data in clinical practice led stakeholders to refrain from utilizing MAA approaches (Bouvy et al., 2018). Besides, risk-sharing agreements can be challenging to implement due to their logistical complexities and the resources required, but also, may not be able to meet their goal of clearing uncertainty. A review of conditional financing agreements in the Netherlands (2006–2012) showed that, in 41% of cases, the data on effectiveness obtained were insufficient to draw conclusions, in 50% additional conditions were required, and in 17% cases there were reasons that advised to suspend reimbursement, but this was unfeasible to implement (Makady et al., 2019b).

Collaboration and early dialogue between stakeholders, including patients, is also crucial to manage expectations and to ensure that access mechanisms are transparent and appropriate (Simoens et al., 2022). The new scenario of accepted uncertainty in some relevant therapeutic areas, such as oncology and orphan diseases, will require further innovative approaches that account for such uncertainty in quantifying therapeutic added value and

price. Thus, European countries have adopted different mechanisms for addressing these challenges in oncology. These include approaches aimed directly at the issue, such as multi-year-multi-indication agreements, flexible access agreements for new indications with clinical uncertainty, development of a new agreement for each new indication, and immediate access for new indications and bundled assessments. It is important that policymakers, payers and manufacturers engage in early discussions and are willing to find new solutions to manage appropriately decision on access to innovative medicines (Lawlor et al., 2021).

The Oslo Medicines Initiative (OMI) is a collaborative effort between the WHO Regional Office for Europe, the Norwegian Ministry of Health and Care Services, and the Norwegian Medicines Agency. The OMI aims to provide a neutral platform for the public and the private sectors to jointly outline a vision for equitable and sustainable access to and affordability of effective, novel and high-priced medicines, OMI in a technical report summarizes existing policy options for payers that support innovation and access to medicines in the WHO European Region. It identifies various tools, such as early assessment schemes, managed entry agreements, and innovation funds in 48 countries. The report describes methods for generating evidence and manage access to innovation, such as value-based pricing, pooled procurement, and subscription fee-based procurement. It also acknowledges potential limitations of the identified policies, such as financial sustainability of healthcare systems and trade-offs between incentivizing innovation and principles of evidence generation, transparency, and budget impact (Vogler, 2022).

The health and economic impact of making decisions on access to innovative medicines with limited evidence are significant, and it is essential communicating these issues more effectively to the public. Medicines regulation is designed to protect public health, and the requirement of robust evidence is an ethical obligation to ensure that new treatments are safe and effective. The decision-making process on the price and financing of these innovative medicines must be transparent and based on efficacy, efficiency and affordability, to ensure best use of resources and health system sustainability. Both are safety measures aimed to improve the good for the most, acting as filters rather than barriers, and it would be desirable to ensure that this is perceived as such by the public. Filters are a necessary step to ensure that innovative medicines are safe and effective and that they provide value for money, rather than being bureaucratic obstacles to access. A better communication can help to build a more informed and engaged society, trusting and empowering bodies in charge of veiling for public interests, and ultimately improve public health outcomes.

5 Conclusion

In summary, while the EU regulatory process for access to medicines with limited evidence demonstrates flexibility in addressing rare diseases and unmet medical needs, it also introduces substantial clinical uncertainty for public system payers regarding the efficacy and safety of marketed medicines. The consequence of this is uncertainty about the therapeutic place of these drugs in clinical practice, difficulties in making decisions about the price and financing of medicines, and increased budgets for spending on drugs with little evidence.

Based on the above concepts, it is recommended to ensure a balance between flexibility in order to facilitate access to medicines for rare diseases and unmet medical needs, and the need for rigorous clinical research to provide evidence of safety and efficacy at reasonable and affordable prices in order to make the health system sustainable. This could involve implementing well designed clinical trial and gathering post-marketing real world data for innovative medicines granted accelerated authorization, as well as the implementation of a balanced P&R system, through a transparent price regulation, evidence-based approach withprices proportional to the strength and level of evidence and value-based pricing or managed access agreements.

Lastly, it is crucial to communicate the reasoning behind regulatory and financing decisions in a balanced manner. Presently, when regulatory and financing entities seek substantial evidence to guarantee the efficacy, safety, and efficiency of new innovative treatments, the messaging conveyed by media to healthcare professionals and the broader society often frames it as “barriers to innovation”. While there is always area for improvement in procedural efficiency, it is important to visualize the role of public administration bodies in pursuing the best interest for the most. An excessive simplification of messages may push political decisions on access in absence of guarantees on efficacy and safety of those innovative medicines that eventually could be against the general interest. New treatments must be made available to patients as soon as possible, but in a safe, efficient and responsible way. Being fast should not mean rushing but being more responsive. In the fast-paced world of modern medicine, it is easy to get caught up in the race for speed and efficiency. However, true progress lies in balancing speed with accuracy, and we must strive to move forward quickly without sacrificing the essential elements of patient care.

Author contributions

Concept and design: AV, CP, and AA; Drafting and revising the manuscript, AV; Critical revision of the paper for important intellectual content: AV, CP, and AA. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 07 September 2023
DOI 10.3389/fphar.2023.1219694

OPEN ACCESS

EDITED BY
Atse Huisman,
Health Insurers Netherlands, Netherlands

REVIEWED BY
Mohamed El Alili,
VU Amsterdam, Netherlands
Antonino Maniaci,
University of Catania, Italy

*CORRESPONDENCE
Meisheng Lei,
2376537605@qq.com
Ruijia Chen,
ruijiachen503@163.com

†These authors have contributed equally to this work

RECEIVED 09 May 2023
ACCEPTED 28 August 2023
PUBLISHED 07 September 2023

CITATION
He Y, Lin W, Cai Z, Huang Y, You M, Lei M and Chen R (2023), Cost-effectiveness analysis of transarterial chemoembolization combined with lenvatinib as the first-line treatment for advanced hepatocellular carcinoma. *Front. Pharmacol.* 14:1219694. doi: 10.3389/fphar.2023.1219694

Cost-effectiveness analysis of transarterial chemoembolization combined with lenvatinib as the first-line treatment for advanced hepatocellular carcinoma

Ying He[1†], Wangchun Lin[2†], Zhongjie Cai[2], Yufan Huang[2], Maojin You[2], Meisheng Lei[2*] and Ruijia Chen[3*]

[1]Department of Emergency Medicine, Mindong Hospital Affiliated to Fujian Medical University, Ningde, Fujian, China, [2]Department of Pharmacy, Mindong Hospital Affiliated to Fujian Medical University, Ningde, Fujian, China, [3]Department of Pharmacy, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, Fujian, China

Purpose: Results from the LAUNCH trial suggest transarterial chemoembolization (TACE) in combination with lenvatinib is significantly more effective than lenvatinib as a first-line treatment option for advanced hepatocellular carcinoma (HCC). However, the cost of TACE is substantial. This study compares the cost-effectiveness of TACE in combination with lenvatinib (TACE-LEN) with that of lenvatinib alone as the first-line treatment for advanced HCC from the perspective of the Chinese healthcare system.

Methods: Markov models of different health states were constructed to simulate first-line treatment, disease progression, and survival in patients with advanced HCC. Clinical efficacy was obtained from the LAUNCH trial. The cost of drugs was sourced from national tender prices, and the treatment cost of weight-decreased was obtained from the Fujian Provincial Bureau of Prices. Other costs and utility values were based on the published literature. Total costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) comprised the model output. One-way and probabilistic sensitivity analyses were performed to validate model robustness and subgroup analyses were also conducted.

Results: Analysis of the model showed that compared to lenvatinib, TACE-LEN improved effectiveness by 1.60 QALYs at a total cost increase of $48,874.69, with an ICER value of $30,482.13/QALY. A one-way sensitivity analysis found that the progression-free survival utility value per year had the greatest impact on the model. A probabilistic sensitivity analysis showed that TACE-LEN had a 97.9% probability of being cost-effective as the first-line treatment option for advanced HCC compared to lenvatinib when the willingness-to-pay (WTP) value was $38,201/QALY (three times the Chinese GDP *per capita* in 2022). Subgroup analysis showed that all subgroups of patients preferred TACE-LEN. However, when the WTP threshold was below $30,300/QALY, TACE-LEN is no longer cost-effective.

Conclusion: Our study found TACE-LEN to be a cost-effective treatment option for patients with advanced HCC compared to lenvatinib from a Chinese healthcare system perspective, but not so in low-income provinces in China.

KEYWORDS

cost-effectiveness, transarterial chemoembolization, hepatocellular carcinoma, first-line treatment, TACE-LEN, lenvatinib

1 Introduction

Primary liver cancer is one of the most frequent malignant tumors in the world, ranking as the sixth most common cancer and the third leading cause of cancer-related deaths. Approximately 906,000 new diagnoses and 830,000 deaths occurred due to liver cancer in 2020 alone (Sung et al., 2021). In China, the incidence and mortality rate of primary liver cancer ranks fourth and second, respectively, in the category of malignancies (Chen et al., 2016). Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for approximately 90% of cases (Llovet et al., 2021). China is also one of the high-risk regions for HCC (Sung et al., 2021). Most patients are diagnosed with HCC which has progressed to an advanced stage and is no longer amenable to radical treatments such as surgery (Forner et al., 2018). Lenvatinib, an oral tyrosine kinase inhibitor, is recommended as the standard first-line treatment for advanced HCC (Chen et al., 2020). Unfortunately, the efficacy of lenvatinib is unsatisfactory, with a median overall survival (OS) of only 13.6 months when administered as the first-line treatment for advanced HCC (Kudo et al., 2018).

Transarterial chemoembolization (TACE) is majorly used for the palliative treatment of patients with advanced HCC (Wu et al., 2017). However, a considerable number of patients are insensitive or resistant to TACE alone (Kudo et al., 2014), probably due to the upregulation of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) after TACE is performed (Sergio et al., 2008). Lenvatinib is an anti-angiogenic drug that can inhibit VEGF and FGF, thus inhibiting tumor angiogenesis and tumor cell proliferation (Kudo, 2018). In addition, TACE may improve the antitumor activity of lenvatinib by reducing the tumor load (Lencioni et al., 2016; Peng et al., 2022). Therefore, the synergistic anti-tumor properties of TACE and lenvatinib appear promising. A recent study in China (LAUNCH trial) evaluated the efficacy and safety of TACE in combination with lenvatinib (TACE-LEN) for the treatment of advanced HCC (Peng et al., 2022). TACE-LEN significantly prolonged median overall survival (OS) (17.8 vs. 11.5 months) and median progression-free survival (PFS) (10.6 vs. 6.4 months) in patients with advanced HCC compared to lenvatinib and was associated with only mild adverse effects (Peng et al., 2022). Thus, the findings of the LAUNCH trial bring hope to patients with advanced HCC, but the high cost of TACE also carries a heavy economic burden on patients and the national healthcare system. To the best of our knowledge, there are presently no economic evaluations of TACE-LEN for advanced HCC. In our study, we used Markov models to perform a pharmacoeconomic evaluation of the two treatment strategies (TACE-LEN vs. lenvatinib) for the treatment of advanced HCC, from a Chinese healthcare system perspective.

2 Materials and methods

The study was designed following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines (Supplementary Table SA) (Husereau et al., 2022).

2.1 Model structure

A Markov model was developed using TreeAge Pro 2022 (TreeAge Software, Williams-town, MA) to compare the cost-effectiveness of two regimens (TACE-LEN vs. lenvatinib) as the first-line treatment for advanced HCC. The model included four different health states: PFS, recurrence-free survival (RFS), progressive disease (PD), and death. All the health states were mutually exclusive (Figure 1). All patients were in the PFS state at the start of treatment, and as treatment progressed, patients were allowed to remain in their current health state or move to the next health state. Patients were not allowed to return to their previous healthy state. The time horizon of the model was approximately 11 years (determined as the time point at which 99% of the patients in the cohort died), with each cycle in the model being 21 days. Our cost-effectiveness analysis was conducted from the perspective of the Chinese healthcare system. The model output included total cost, life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). We set the willingness-to-pay (WTP) threshold to $38,201/QALY (three times the GDP *per capita* in China in 2022), as recommended by the World Health Organization (Cameron et al., 2018; Ochalek et al., 2020). If the ICER value was lower than the predefined WTP threshold, we then considered TACE-LEN to be cost-effective compared to lenvatinib as the first-line regimen for advanced HCC.

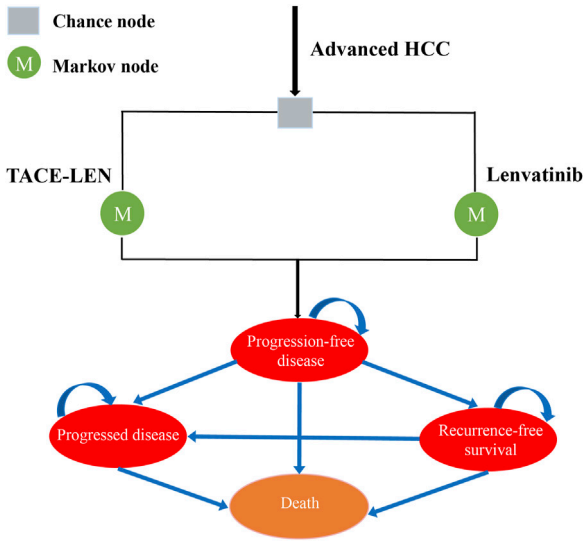

FIGURE 1
Markov model simulating outcomes for the LAUNCH trial. All patients with advanced HCC started with PFS state and received treatment with TACE-LEN or lenvatinib. HCC, hepatocellular carcinoma; TACE-LEN, transarterial chemoembolization in combination with Lenvatinib.

TABLE 1 The basic parameters of the input model and the range of sensitivity analyses.

Variable	Base Value	Range		Distribution	Source
		Min	Max		
Log-logistic survival model of PFS for lenvatinib group					
Scale (λ)	0.1524227	0.121938	0.182907	Log-logistic	Peng et al. (2022)
Shape (γ)	2.850079	2.2800632	3.4200948	Log-logistic	Peng et al. (2022)
Log-logistic survival model of OS for lenvatinib group					
Scale (λ)	0.08526536	0.068212	0.102318	Log-logistic	Peng et al. (2022)
Shape (γ)	2.926645	2.341316	3.511974	Log-logistic	Peng et al. (2022)
HR of TACE-LEN group versus lenvatinib group					
HR for PFS	0.43	0.34	0.60	Log-normal	Peng et al. (2022)
HR for OS	0.45	0.33	0.60	Log-normal	Peng et al. (2022)
TACE-LEN group: incidence of AEs					
Hyperbilirubinemia	0.094	0.075	0.113	Beta	Peng et al. (2022)
Elevated ALT/AST	0.406	0.325	0.487	Beta	Peng et al. (2022)
Weight decreased	0.076	0.061	0.091	Beta	Peng et al. (2022)
Hypertension	0.206	0.165	0.247	Beta	Peng et al. (2022)
Diarrhea	0.053	0.042	0.064	Beta	Peng et al. (2022)
Lenvatinib group: incidence of AEs					
Hyperbilirubinemia	0.030	0.024	0.036	Beta	Peng et al. (2022)
Elevated ALT/AST	0.030	0.024	0.036	Beta	Peng et al. (2022)
Weight decreased	0.071	0.057	0.085	Beta	Peng et al. (2022)
Hypertension	0.196	0.157	0.235	Beta	Peng et al. (2022)
Diarrhea	0.042	0.034	0.050	Beta	Peng et al. (2022)
Cost ($)					
Hyperbilirubinemia	124.90	99.92	149.88	Gamma	Wen et al. (2021)
Elevated ALT/AST	45.60	36.48	54.72	Gamma	Li et al. (2021)
Weight-decreased	75.20	60.16	90.24	Gamma	Local charge
Hypertension	1.48	1.18	1.78	Gamma	Wen et al. (2021)
Diarrhea	3.61	2.89	4.33	Gamma	Wen et al. (2021)
Hepatectomy	9058.24	7246.59	10869.89	Gamma	Zhang et al. (2022)
Hospitalization per cycle	384.00	307.20	460.80	Gamma	Zhang et al. (2022)
TACE per cycle	1929.00	1543.20	2314.80	Gamma	Zhang et al. (2022)
BSC per cycle	363.00	290.40	435.60	Gamma	Zhang et al. (2022)
Test per cycle	359.96	287.97	431.95	Gamma	Li et al. (2021)
End-of-life care	2176.00	1740.80	2611.20	Gamma	Kang et al. (2021)
Lenvatinib	1054.88	843.90	1265.86	Gamma	Yao (2023)
Utility value					
PFS	0.76	0.608	0.912	Beta	Li et al. (2021)
PD	0.68	0.544	0.816	Beta	Li et al. (2021)

(Continued on following page)

TABLE 1 (*Continued*) The basic parameters of the input model and the range of sensitivity analyses.

Variable	Base Value	Range		Distribution	Source
		Min	Max		
RFS	0.76	0.608	0.912	Beta	Li et al. (2021)
Discount rate (%)	5.00	0.00	8.00	Fixed	Liu et al. (2011)
Proportion					
Undergoing hepatectomy after TACE-LEN	0.153	0.122	0.184	Beta	Peng et al. (2022)
Undergoing hepatectomy after lenvatinib	0.018	0.014	0.022	Beta	Peng et al. (2022)
Recurrence of HCC	0.19	0.15	0.20	Beta	Zheng et al. (2017), Zhang et al. (2022)

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; BSC, best supportive care; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; PD, progression of disease; PFS, progression-free survival; RFS, recurrence-free survival; TACE, transarterial chemoembolization; TACE-LEN, transarterial chemoembolization in combination with Lenvatinib.

2.2 Clinical data

Patients included were consistent with the population characteristics of the LAUNCH trial (Peng et al., 2022), a randomized phase III clinical trial conducted in 12 hospitals in China from June 2019 to July 2021 with the following criteria: 1) age 18–75 years; 2) advanced primary HCC without any previous treatment or advanced HCC that has not received any postoperative treatment after hepatectomy and has recurred for the first time; 3) at mRECIST19 basis, with at least one measurable lesion in the liver; intrahepatic lesions consisting of a single tumor or multiple tumors with 50% tumor burden; 4) Eastern Cooperative Oncology Group performance status score of 0 or 1; 5) Child-Pugh class A; 6) life expectancy of 3 months or more. These patients were randomly assigned to receive either TACE-LEN or lenvatinib. To simplify the model, we assumed that all patients took 12 mg of lenvatinib daily and were discontinued when disease progression or unacceptable toxicity occurred. Patients in the TACE-LEN group started TACE treatment 1 day after oral lenvatinib and underwent TACE again if incomplete necrosis and tumor regeneration were detected. TACE was discontinued if disease progression occurred or it could not be administered. Economic analyses were based on published randomized clinical trials and mathematical models. As a result, institutional review board or ethics committee approval was not necessary for this study.

2.3 Transition probabilities

The probabilities of PFS and OS in Kaplan–Meier survival curves of patients in the lenvatinib group from the LAUNCH trial (Peng et al., 2022) were extracted by GetData Graph Digitizer (version 2.26) (Wan et al., 2019). Individual patient data for each Kaplan–Meier curve were reconstructed and the data were fitted using R software (version 4.2.0) using survival extrapolation to obtain long-term clinical survival functions, according to the method described by Hoyle and Henley (2011). The best-fit survival functions were selected based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC) tests, in that lower AIC and BIC values indicated a better fit (Williams et al., 2017). The AIC and BIC values for each type of survival distribution function for PFS and OS curves are shown in Supplementary Table SB; Supplementary Figure SA. Also, external validation of our extrapolated survival function was performed using the results of Kudo et al. (2018a) according to the method of Latimer (2013). Ultimately, the log-logistic distribution function [$S(t)=(1+(\lambda t)^{\gamma})^{-1}$; S: survival probability, t: time cycle, λ: scale parameter, and γ: shape parameter] provided the best fit for the PFS and OS data of the patients in the lenvatinib group and was used to generate the probability of transition for the lenvatinib strategy (Table 1; Figure 2). The PFS and OS data for the TACE-LEN group were calculated based on the hazard ratio (HR) for the TACE-LEN group versus that for the lenvatinib group as reported in the LAUNCH trial (Peng et al., 2022). In the LAUNCH trial (Peng et al., 2022), after the institution of the first-line treatment, 15.3% and 1.8% of patients in the TACE-LEN and lenvatinib groups, respectively, underwent hepatectomy due to down-staging, and these patients subsequently entered RFS status, while those with recurred after hepatectomy entered PD status. Because the LAUNCH trial (Peng et al., 2022) did not provide data on the risk of recurrence of HCC after hepatectomy, we assumed a 5-year recurrence rate of 19% after hepatectomy in the model as reported by Zheng et al. (2017). Meanwhile, the 7-year (20%) and 3-year (15%) recurrence rates were used as the upper and lower bounds for sensitivity analysis, respectively (Zheng et al., 2017; Li et al., 2021; Zhang et al., 2022). We assumed that the transition probability from the PFS state to the death state is the natural mortality rate of the Chinese population in 2022 (7.4‰) (Compiled by National Bureau of Statistics of China, 2023). All patients received the best supportive care (BSC) after disease progression, including aggressive analgesia, correction of hypoalbuminemia, intensive nutritional support, and management of complications such as ascites, jaundice, and hepatic encephalopathy (The General Office Of The National Health and Health Commission, 2022).

2.4 Costs and health utility values

We considered only direct medical costs in our model, including the costs of drugs, hospitalization, tests, hepatectomy, end-of-life

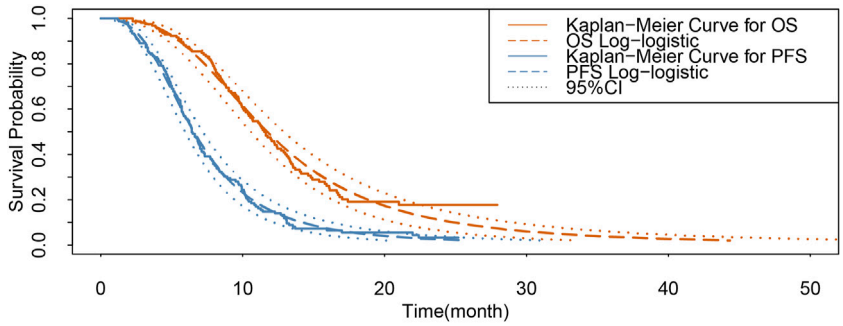

FIGURE 2
Results of the survival curve fit the lenvatinib group. 95% CI: 95% confidence interval; OS, overall survival; PFS, progression-free survival.

care, management of adverse reactions with an incidence greater than 5%, and BSC (Table 1). Based on the LAUNCH trial (Peng et al., 2022), patients in the TACE-LEN group received a mean of three TACE treatments, and patients in the lenvatinib group received lenvatinib for an average duration of 5.1 months (approximately 7 cycles). The treatment cost of weight decreased adverse reaction was taken from the Fujian Provincial Price Bureau, and the cost of drugs was from the national tender price. Other costs were sourced from published literature and adjusted to 2022 values using the China Statistics Bureau Medical Price Index (Compiled by National Bureau of Statistics of China, 2023). All costs are expressed in US dollars, converted at the average exchange rate in 2022 ($1 = 6.73 RMB). Health-related quality of life was extracted to calculate cost-effectiveness in each group. Since quality of life was not assessed in the LAUNCH trial, we obtained the utility values (EQ-5D) for PFS, RFS, and PD from the National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance 189 (NICE, 2017) and published literature (Cammà et al., 2013; Qin et al., 2018; Li et al., 2021; Zhang et al., 2022). Both costs and utility values were discounted, and the discounted value was set at 5% per year (Liu G et al., 2011).

2.5 Model results and sensitivity analysis

Total cost, LYs, QALYs, and ICERs constituted the model output. To identify the variables that have the greatest influence on the model outputs, we conducted a one-way sensitivity analysis, the results were represented as a tornado diagram, we let the value of each variable in the model fluctuate at a certain level, and the fluctuation range was derived from published literature. The variation range used ±20% of the baseline value in the absence of data. The lower and upper values of the discount rate were set at 0% and 8%, respectively (Liu G et al., 2011). In addition, to verify the influence of the parameters on the uncertainty of the model, we performed a probabilistic sensitivity analysis with Monte Carlo simulations of the model with 1,000 replications. To this end, specific distributions of the parameters were chosen as appropriate, as shown in Table 1. The results of the probabilistic sensitivity analysis are represented by cost-effectiveness acceptability curves and scatter plots. At the same time, we explore the changes in the TACE-LEN cost-effectiveness probability by continuously reducing the WTP threshold to meet the needs of Chinese provinces, which differ significantly from each other in terms of their economic development levels.

2.6 Subgroup analysis

We performed a subgroup analysis of all patients using the method prescribed by Hoyle et al. (2010) using specific HRs of subgroups reported in the LAUNCH trial (Table 2) (Peng et al., 2022).

2.7 Scenario analysis

We analyzed five different scenarios across the overall population. Firstly, we set different 5-year recurrence probabilities after HCC surgery (15%, 20%) to assess the impact of postoperative recurrence rates on the model outcomes. Secondly, the model's time horizon was varied to 3 years, 5 years, and 7 years to evaluate its robustness as much as possible. Thirdly, we assumed that only 80% or 50% of patients received BSC after disease progression, simulating some patients in clinical practice who discontinue treatment due to certain reasons. Fourth, the daily dosage of lenvatinib for all patients has been changed to 8 mg or 10 mg. Fifth, in the base case analysis, we made the conservative assumption that the probability of a patient dying directly from PFS status was assumed to be equal to the natural mortality rate in the Chinese population. To assess the impact of this assumption on the model results, we conducted a scenario 5 analysis. In this scenario, we adjusted the probability that a patient with PFS state would die outright by setting it at 2 or 4 times the natural mortality rate of the Chinese population.

3 Results

3.1 Base case analysis

The results of the cost-effectiveness analysis of the model are shown in Table 3. The lenvatinib group obtained 1.57 LYs and

TABLE 2 Results for subgroup analyses.

Subgroup	PFS HR (95% CI)	OS HR (95% CI)	ICER ($/QALY)	Cost-effectiveness probability (%)
Age, years				
60 and younger	0.37 (0.27–0.50)	0.42 (0.29–0.61)	31,234.18	96.7
older than 60	0.55 (0.35–0.84)	0.52 (0.30–0.89)	29,046.99	98.0
Sex				
Male	0.43 (0.33–0.56)	0.43 (0.31–0.60)	30,422.54	97.4
Female	0.46 (0.27–0.80)	0.52 (0.27–1.00)	30,085.37	96.0
Bodyweight, kg				
<60	0.42 (0.28–0.64)	0.46 (0.28–0.76)	30,582.50	96.4
≥60	0.44 (0.32–0.59)	0.43 (0.30–0.63)	30,277.62	96.6
Aetiology				
HBV	0.43 (0.33–0.56)	0.47 (0.34–0.64)	30,523.71	97.1
Others	0.44 (0.22–0.89)	0.34 (0.15–0.78)	29,822.47	97.2
ECOG–PS				
0	0.46 (0.33–0.64)	0.40 (0.26–0.62)	29,946.08	98.7
1	0.33 (0.22–0.48)	0.45 (0.29–0.70)	31,945.73	93.3
AFP, ng/mL				
<400	0.53 (0.38–0.75)	0.50 (0.33–0.77)	29,304.15	98.4
≥400	0.35 (0.25–0.51)	0.39 (0.26–0.61)	31,421.92	93.9
ALBI grade				
Grade 1	0.36 (0.22–0.58)	0.47 (0.27–0.82)	31,471.43	93.0
Grade 2	0.46 (0.34–0.61)	0.44 (0.31–0.63)	30,039.09	98.1
No. of tumor				
Single	0.44 (0.25–0.76)	0.55 (0.27–1.11)	30,365.88	94.0
Multiple	0.44 (0.34–0.58)	0.43 (0.31–0.60)	30,278.26	97.2
Main tumor size, cm				
<5	0.46 (0.29–0.73)	0.38 (0.20–0.71)	29,848.91	97.2
≥5	0.42 (0.32–0.56)	0.47 (0.33–0.66)	30,658.87	95.2
Primary tumor				
Yes	0.44 (0.34–0.57)	0.44 (0.32–0.61)	30,318.34	97.3
No	0.37 (0.16–0.86)	0.30 (0.07–1.34)	30,690.05	96.3
PVTT				
Yes	0.31 (0.23–0.41)	0.34 (0.24–0.49)	31,880.65	93.1
No	0.67 (0.43–1.05)	0.72 (0.40–1.29)	27,746.96	98.5
EHS				
Yes	0.46 (0.33–0.63)	0.56 (0.38–0.82)	30,274.72	97.2
No	0.40 (0.28–0.59)	0.32 (0.19–0.52)	30,426.26	97.4

AFP, a-fetoprotein; ALBI, albumin-bilirubin score; ECOG-PS, eastern cooperative oncology group performance status; EHS, extrahepatic spread; HBV, hepatitis B virus; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PVTT, portal vein tumor thrombus; QALY, quality-adjusted life years; TACE, transarterial chemoembolization.

TABLE 3 Main results of the model output.

Regimen	TACE-LEN	Lenvatinib	Incremental
Overall cost ($)	86,254.63	37,379.93	48,874.69
Overall LYs	4.17	1.57	2.60
Total QALYs	2.65	1.05	1.60
ICER, ($)			
per LY			18,800.48
per QALY			30,482.13

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; TACE-LEN, transarterial chemoembolization in combination with Lenvatinib.

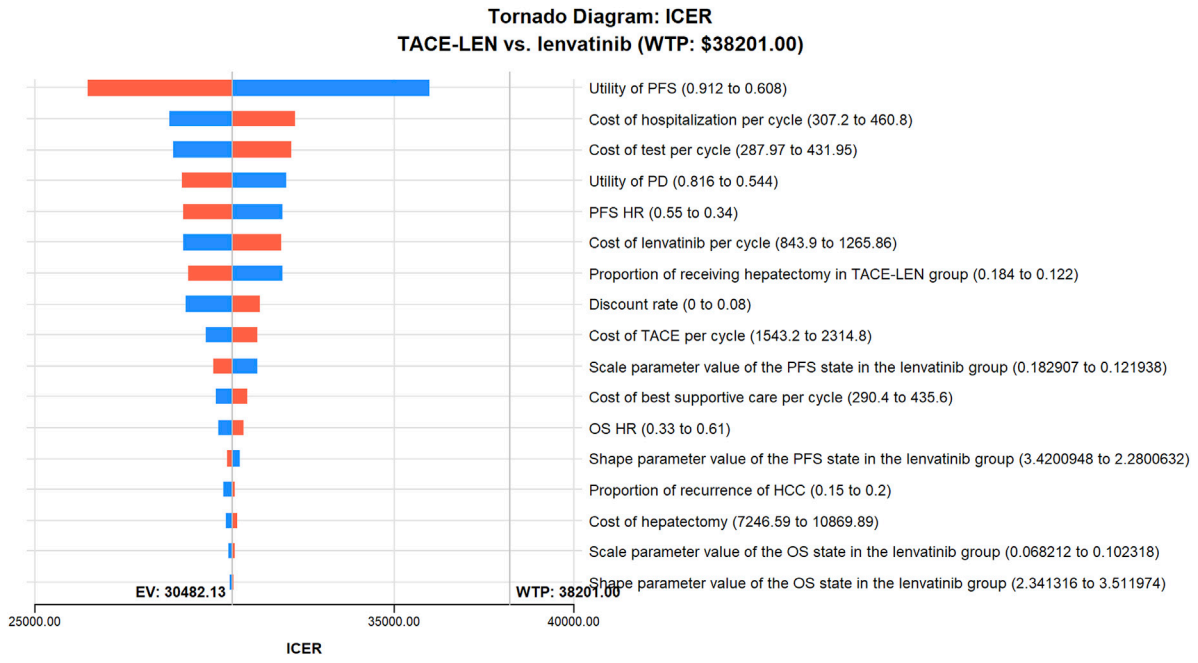

FIGURE 3
One-way sensitivity analyses of TACE-LEN in comparison with lenvatinib. HCC, hepatocellular carcinoma; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progression of disease; PFS, progression-free survival; QALY, quality-adjusted life year; TACE, transarterial chemoembolization; TACE-LEN, transarterial chemoembolization in combination with lenvatinib; WTP, willingness-to-pay.

1.05 QALYs at a total cost of $37,379.93, while the TACE-LEN group obtained 4.17 LYs and 2.65 QALYs at a total cost of $51,333.21. Compared to the lenvatinib group, the TACE-LEN group had an ICER value of $30,482.13/QALY, which was lower than the predetermined WTP value ($38,201/QALY). In other words, compared to Lenvatinib, TACE-LEN was found to be a cost-effective treatment option as the first-line regimen for advanced HCC.

3.2 Sensitivity analysis

As per the results of the one-way sensitivity analysis (Figure 3), parameters with the greatest impact on the model results included the PFS utility value per year, the proportion of the TACE-LEN group undergoing hepatectomy, and the discount rate per year. Meanwhile, parameters with a lesser impact on the model results included the cost of the test per cycle, the cost of lenvatinib per cycle, and the cost of hospitalization per cycle. Although these parameters had some impact on the model results, the ICER was consistently lower than the predetermined WTP value ($38,201/QALY) when these parameters were varied within a predetermined range. The results of the probabilistic sensitivity analysis are shown in Figure 4; Supplementary Figure SB. The cost-effectiveness acceptability curve shows that the probability of cost-effectiveness of TACE-LEN increased as the WTP threshold increased. Moreover, when the WTP threshold reached our pre-set threshold ($38,201/QALY), the probability of TACE-LEN being cost-effective as the first-line regimen for HCC was 97.9%.

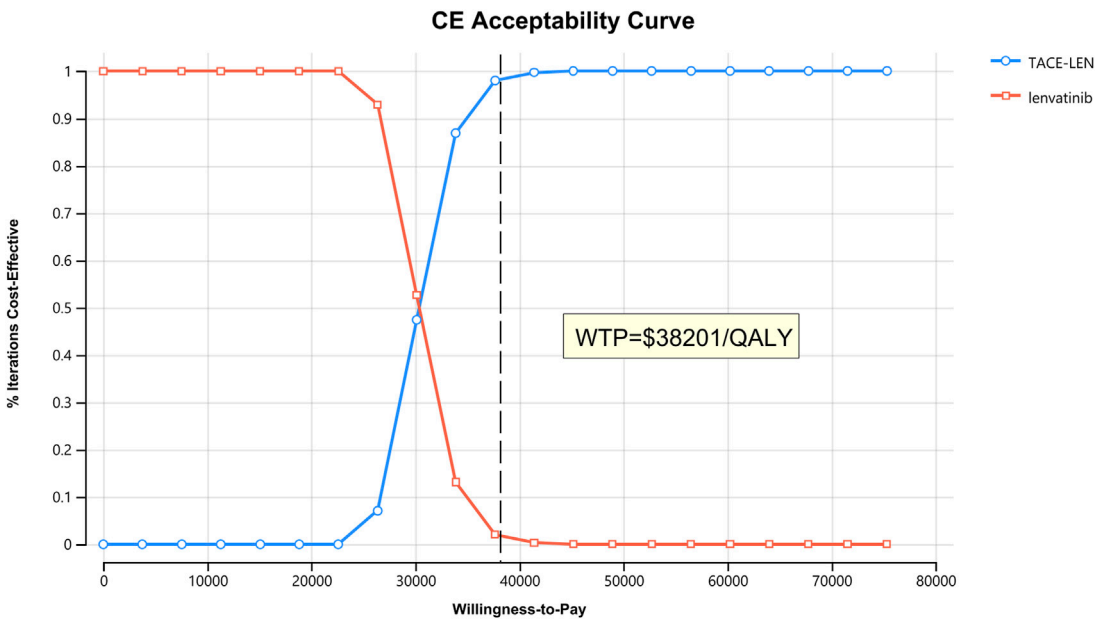

FIGURE 4
The cost-effectiveness acceptability curves for the TACE-LEN treatment option compared with the lenvatinib treatment option. QALY, quality-adjusted life year; TACE-LEN, transarterial chemoembolization in combination with lenvatinib; WTP, willingness-to-pay.

TABLE 4 Results for scenario analyses of the overall population.

Scenarios	Cost ($)		QALY		ICER ($/QALY)
	TACE-LEN	Lenvatinib	TACE-LEN	Lenvatinib	
Scenario 1					
Recurrence of HCC = 0.15	86,581.33	37,405.30	2.68	1.05	30,224.53
Recurrence of HCC = 0.20	86,172.75	37,373.56	2.65	1.05	30,547.07
Scenario 2					
Model runtime (year) = 3	64,869.54	34,819.84	1.73	0.94	37,978.51
Model runtime (year) = 5	75,380.32	36,299.27	2.14	1.00	34,337.91
Model runtime (year) = 7	80,256.90	36,831.81	2.36	1.03	32,549.85
Scenario 3					
80% of patients receive BSC	84,560.74	36,393.04	2.65	1.05	30,041.19
50% of patients receive BSC	82,019.91	34,912.71	2.65	1.05	29,379.78
Scenario 4					
Receive a daily dose of lenvatinib (mg) = 8	78,853.94	33,647.44	2.65	1.05	29,702.73
Receive a daily dose of lenvatinib (mg) = 10	82,549.84	35,511.45	2.65	1.05	31,094.91
Scenario 5					
Probability of direct death in patients with PFS state = 14.8‰	81,541.35	35,334.80	2.61	1.04	29,498.16
Probability of direct death in patients with PFS state = 29.6‰	79,615.02	34,990.08	2.53	1.03	29,817.47

BSC, best supportive care; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; TACE-LEN, transarterial chemoembolization in combination with Lenvatinib; QALY, quality-adjusted life year.

3.3 Subgroup analysis

The results of the subgroup analysis showed that TACE-LEN was cost-effective at a WTP threshold of $38,201/QALY when compared to lenvatinib as a first-line treatment option for advanced HCC, regardless of the baseline characteristics of the patients (Table 2). This further validates TACE-LEN was a cost-effective first-line treatment option for advanced HCC.

3.4 Scenario analysis

In scenario 1, we found that the change in recurrence rate after HCC had little effect on the ICER. In scenario 2, the model's time horizon changes to 3, 5, and 7 years, and the ICERs are $37,978.51/QALY, $34,337.91/QALY, and $32,549.85/QALY, respectively, which shows that as the model runs longer, the ICER value decreases, meaning that the LEN-TACE regimen is more cost-effective. In scenario 3, the ICERs for LEN-TACE versus lenvatinib were $30,041.191/QALY and $29,379.78/QALY, respectively, when 80% or 50% of patients received BSC. In scenario 4, when patients took lenvatinib at a dose of 8 mg or 10 mg per day, the ICERs for TACE-LEN compared to lenvatinib were $29702.731/QALY and $31094.91/QALY, respectively. In scenario 5, when the probability of a patient dying directly from PFS state was 14.8‰ or 29.6‰ per year, the ICERs for TACE-LEN compared to lenvatinib were $29,498.16/QALY and $29,817.47/QALY, respectively. The results of the scenario analysis are shown in Table 4.

4 Discussion

For many years, although there are many treatment options for HCC, such as sorafenib and lenvatinib, the true clinical benefit obtained from these therapeutic regimens has been less than satisfactory, and researchers have been working on exploring new drugs or treatment modalities (Ho et al., 2018; Peng et al., 2022). TACE is the basic treatment for mid to late-stage HCC, and its short-term efficacy is very good, but its long-term efficacy is not satisfactory (Palmer et al., 2020). The emergence of targeted and immunotherapy has enriched the treatment of liver cancer, and the addition of targeted and immunotherapy to TACE can allow patients to achieve longer-term survival. In the choice of a combination therapy regimen, TACE combined with targeted therapy is preferred because the adverse effects of targeted therapy are relatively more controllable. The LAUNCH trial, a randomized phase III study (LAUNCH trial) conducted in China, demonstrated a relative increase in median OS and PFS by 54.8% and 65.6%, respectively, when TACE-LEN was used as a first-line treatment option for patients with advanced HCC compared to lenvatinib monotherapy. Thus, the results of the LAUNCH trial brought new hope to patients with advanced HCC. However, the huge medical costs of TACE are a serious obstacle to its further expansion, thus necessitating a cost-effectiveness analysis of TACE-LEN. The results of our analysis showed that TACE-LEN was a cost-effective treatment option as the first-line therapy for advanced HCC compared with lenvatinib, at a WTP threshold of $38,201/QALY. The probability sensitivity analysis showed a 96.8% probability of cost-effectiveness, and the results of the subgroup analysis also support this cost-effectiveness finding. In addition, the participation rate of residents' health insurance has now reached 96.8% in China. In addition, the participation rate of residents' medical insurance in China has currently reached 96.8%. To our knowledge, this is the first cost-effectiveness analysis of TACE-LEN.

The reimbursement ratio for medical expenses incurred by medical insurance patients in tertiary hospitals is approximately 70%, with a higher percentage in primary healthcare institutions (Qin et al., 2023). Therefore, the actual probability of TACE-LEN being cost-effective may be higher for medical insurance patients. It is important to note that robotic surgery is increasingly being utilized in the treatment of HCC. It enhances surgical precision, reduces invasiveness, and assists surgeons in accessing hard-to-reach areas while minimizing blood loss and promoting faster recovery (Di Luca et al., 2020; Zhu et al., 2023). This holds particular benefits for patients with TACE-LEN treatment. In addition, the collapsibility of the inferior vena cava, a major conduit for deoxygenated blood returning to the heart, can be evaluated using subcostal and trans-hepatic ultrasound imaging. This assessment modality exhibits the potential for assessing the fluid status of patients with advanced HCC, warranting further investigation in this area (Sanfilippo et al., 2023; Zawadka et al., 2023).

Up till now, only two pharmacoeconomic studies had compared TACE with other treatment modalities for advanced HCC (Chen et al., 2018; Zhang et al., 2022), both of which used TACE alone as the therapeutic modality. The study by Zhang et al. (2022) showed that compared to hepatic arterial infusion chemotherapy, TACE was not cost-effective as a first-line treatment option for large unresectable HCC. Similarly, Chen et al. (2018) reported that TACE was not cost-effective as a first-line treatment option for advanced HCC compared with full-dose or dose-adjusted sorafenib. The possible reasons for the inconsistency of these results with our study are that treatment with TACE alone usually makes complete tumor necrosis difficult and then creates a secondary hypoxic environment within the residual lesion. Hypoxia stimulates the expression of angiogenic factors such as VEGF and FGF, which induces tumor progression, recurrence, and metastasis (Sergio et al., 2008; Shim et al., 2008; Chen et al., 2022), and subsequently, HCC patients show insensitivity or resistance to TACE leading to poor prognosis (Kudo et al., 2014; Zhong et al., 2021).

The comparison object selection is an important concern while performing cost-effectiveness analysis using the Markov model. According to the guidelines for the diagnosis and treatment of primary HCC, in addition to lenvatinib, atezolizumab plus bevacizumab and sorafenib are also the first-line treatment for advanced HCC. Currently, we lack robust head-to-head trial data to adequately compare the cost-effectiveness of TACE-LEN and various first-line therapies for advanced HCC. A study by Finn et al. (2020) found better OS and PFS outcomes with atezolizumab plus bevacizumab than with sorafenib for the treatment of unresectable HCC. However, the two China-based economic studies found atezolizumab plus bevacizumab to not be cost-effective compared to sorafenib (Hou and Wu, 2020; Wen et al., 2021). In addition, a study by

Cai et al. (2020) found that from the perspective of the Chinese health delivery system, lenvatinib was a cost-effective targeted agent for unresectable HCC when compared to sorafenib. Therefore, we believe that it is reasonable to select lenvatinib as a comparator for the economic analysis of TACE-LEN.

The huge difference in economic development between different provinces in China is a problem that cannot be ignored, and many provinces' GDP *per capita* does not reach the national average, which makes the results of our economic analysis bring some challenges in informing the actual medical work (Li et al., 2021; Zhang et al., 2022). Data from the National Bureau of Statistics show in 2022 that Gansu's GDP *per capita* ($6,684), the lowest in China, is only 52.4% of the national average (Compiled by National Bureau of Statistics of China, 2023). Therefore, we need to explore the probability that TACE-LEN is cost-effective by continuously lowering the WTP threshold to accommodate the needs of provinces with lower levels of economic development. When we lowered the WTP threshold to 79.8% of the original preset level, i.e., $30482.13/QALY, the probability of TACE-LEN being cost-effective was 50%. That is, when three times the *per capita* GDP of a province is less than $30482.13, TACE-LEN is not cost-effective in that province. These results provide some economic reference for the selection of first-line treatment options for advanced HCC in low-income provinces in China.

Our analysis also has several limitations. First, the cost of weight-decreased treatment was as per the local medical price in Fujian, as it is not nationally consistent. Although this may lead to some bias, sensitivity analysis showed that it did not affect the model results. Second, due to the lack of long-term survival data, we used a log-Logistic survival model to infer survival tails beyond the follow-up time frame, which may not accurately reflect real-world conditions. We intend to update our cost-effectiveness analysis when long-term survival data are reported. Third, to simplify the model, we assumed that all patients received a 12 mg daily dose of lenvatinib, which may not correspond to our treatment reality. Nevertheless, the sensitivity analysis showed that the parameters associated with lenvatinib had little effect on the model results. Fourth, when patients experienced disease progression, we chose to put all patients on BSC due to the lack of relevant survival data for the enrolled patients, which may not accurately reflect current clinical practice. We will analyze this further when relevant treatment costs and survival data for patients after progression are available. Fifth, because the LAUNCH trial failed to provide quality-of-life data, the utility values in the model were derived from NICE and published literature, which may have led to bias in our model results. Finally, we considered only grade 3 or higher adverse events with a probability of occurrence greater than 5% in the model. We assumed that low-probability adverse events would not change the conclusions of the study; sensitivity analyses also showed that the economic results were insensitive to parameters related to adverse reactions.

5 Conclusion

Our study found that compared to lenvatinib, TACE-LEN is a cost-effective option as a first-line treatment for advanced HCC from a Chinese healthcare system perspective, but not so in low-income provinces in China. Although TACE-LEN is not currently included as a first-line treatment option as per Chinese HCC guidelines, our findings provide an important economic rationale for Chinese guideline developers, including those in low-income areas, to decide on the suitability of TACE-LEN as a first-line treatment option for advanced HCC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

Study design and supervision: YiH and WL; data analysis and interpretation: ZC and MY; data collection: YuH and ML; manuscript writing: RC; final approval of the manuscript: All authors contributed to the article and approved the submitted version.

Funding

This study was supported in part by grants from the Natural Science Foundation of Fujian Province (Grant number: 2023J011910); Startup Fund for scientific research, Fujian Medical University (Grant number: 2021QH1203); Natural Science Foundation of Ningde (Grant number: 2022J29); Mindong Hospital Science Fund (Grant number: 2022YN005). This study was not supported by any pharmaceutical company.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1219694/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 17 October 2023
DOI 10.3389/fphar.2023.1264997

OPEN ACCESS

EDITED BY
Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani,
CZ Health Insurance, Netherlands

REVIEWED BY
Hong Shen,
Bristol Myers Squibb, United States
Carelle Reparon-Schuijt,
Zilveren Kruis BV, Netherlands

*CORRESPONDENCE
Natalja Bouwhuis,
n.bouwhuis@amsterdamumc.nl

RECEIVED 21 July 2023
ACCEPTED 25 September 2023
PUBLISHED 17 October 2023

CITATION
Bouwhuis N, Jacobs BAW and Kemper EM (2023), Product development and quality of pharmacy compounded chenodeoxycholic acid capsules for Dutch cerebrotendinous xanthomatosis patients.
Front. Pharmacol. 14:1264997.
doi: 10.3389/fphar.2023.1264997

Product development and quality of pharmacy compounded chenodeoxycholic acid capsules for Dutch cerebrotendinous xanthomatosis patients

Natalja Bouwhuis[1,2]*, Bart A. W. Jacobs[1,2] and E. Marleen Kemper[3]

[1]Department of Pharmacy and Clinical Pharmacology, Amsterdam UMC, Amsterdam, Netherlands, [2]Platform Medicine for Society, Amsterdam UMC, Amsterdam, Netherlands, [3]Department of Experimental Vascular Medicine, Amsterdam UMC, Amsterdam, Netherlands

Introduction: In 2017 the drug chenodeoxycholic acid (CDCA) became unavailable to Dutch patients with the rare inborn error of metabolism cerebrotendinous xanthomatosis (CTX). This was a direct result of a steep price increase after CDCA was authorized in the EU as an orphan drug. As a result, Dutch health insurance companies were unable to reimburse this drug and the availability of CDCA to patients with CTX was directly at risk creating an unmet medical need. CTX is characterized by juvenile cataract, tendon xanthomas, infantile-onset diarrhea, psychomotor retardation and progressive cerebellar ataxia. Treatment with CDCA, when initiated before neurological symptoms are present, can prevent the onset of neurological complications.

Methods: To assure continuation of patient treatment with a high quality product, the hospital pharmacy of the Amsterdam UMC developed CDCA capsules as a pharmacy preparation. A simple and robust formulation was developed for capsules in a broad dose range of 35–250 mg, ensuring that both pediatric and adult patients can receive an exact dose tailored to their specific needs. Capsules are prepared manually on a small scale for the individual patient. To assure the quality of the product, product validation and stability studies were performed.

Results: The results show that the product complies with all specifications based on the requirements of the European Pharmacopoeia. The capsules contain the declared amount of CDCA, no degradation product or other (microbiological) impurities are formed during the production process and the capsules show a quick dissolution profile. Stability studies indicate that it is a stable product and no impurities increase or arise over time. These results show that these pharmacy preparations are of high quality and comply to Good Manufacturing Practice (GMP) requirements.

Discussion: Through our research, we have demonstrated that pharmacy compounding can be a viable alternative in situations where immediate access to essential medication is crucial or when certain drugs are temporarily

inaccessible. The purpose of this paper is to offer comprehensive guidance to other pharmacies to improve the availability of currently inaccessible drugs through the practice of pharmacy compounding, thereby facilitating improved patient care.

KEYWORDS

pharmacy preparation, pharmacy compounding, chenodeoxycholic acid, cerebrotendinous xanthomatosis, product validation, stability, good manufacturing practice, European Pharmacopoeia

1 Introduction

Chenodeoxycholic acid (CDCA) is an effective drug in the treatment of cerebrotendinous xanthomatosis (CTX) (Federico and Gallus, 2003). CTX is a rare metabolic disease caused by *CYP27A1* gene mutations leading to reduced plasma levels of bile acids including CDCA, and accumulation of toxic bile acid intermediates such as cholestanol in plasma and tissues. Due to these toxic substances, patients may experience various, often severe, symptoms such as infantile-onset diarrhea, juvenile cataract and tendon xanthomas, and adult onset of neurologic dysfunction (including psychiatric disturbances, cerebellar symptoms, neuropathy and dementia) (Federico and Gallus, 2003). Treatment with CDCA, when initiated before neurological symptoms are present, can prevent the onset of neurological complications (Stelten et al., 2022).

Initially, orally administered CDCA was used to dissolve gallstones. However, this indication has become obsolete (Fiorucci and Distrutti, 2019). Since the 1970s, CDCA treatment is used in CTX patients in the Netherlands in an off-label setting (Dutch National Health Care Institute, 2018). In 2017, CDCA was approved by the European Medicines Agency as an orphan drug for the treatment of CTX (Leadiant GmbH, 2017). After market authorization, the price increased from €30.000 to a list price of around €170.000 per patient per year (Sheldon, 2018; KNMP, 2023). As a consequence of this price increase, the secretary of Healthcare did not provide for a legal basis for reimbursement and Dutch health insurance companies were unable to reimburse the drug, other than a payment by way of courtesy. As a result an essential treatment was no longer available to CTX patients in the Netherlands (Sheldon, 2018).

In order to prevent treatment interruption and to assure CDCA availability, the hospital pharmacy of the Amsterdam UMC developed CDCA capsules by pharmacy preparation, also known as pharmacy compounding or *formula magistralis* (Sheldon, 2018). Pharmacy compounding is often applied when authorized medicines are not available or not suited for patient treatment, for example, when a specific dose is required. The authorized CDCA product, which was not reimbursed, is only available as 250 mg capsules. This formulation is suitable for adult dosing, as they receive a starting dose of 750 mg per day in three divided doses, which can be increased to 1,000 mg per day. However, pediatric patients receive a starting dose of 5 mg/kg per day, in three divided doses, which can be increased to 15 mg/kg per day (Leadiant GmbH, 2017). The smallest required dose for Amsterdam UMC patients was 105 mg per day in three divided doses of 35 mg. CDCA 250 mg capsules are therefore unsuitable for accurate dosing in pediatric patients. On top of that, the large capsule size can be difficult to swallow for pediatric patients. In order to make CDCA capsules available for both pediatric and adult patients, the CDCA capsules were developed and manufactured in a range of 35–250 mg, following applicable good manufacturing practice (GMP) as well as national compounding guidelines (KNMP, 2022). Many hurdles were tackled during this development which are discussed extensively in an article by Polak et al. (2021). In this article we will elaborate on the product validation and stability studies that followed, to demonstrate the quality of the pharmacy compounded CDCA capsules.

2 Materials and methods

2.1 Starting materials

The product formulation consists of the active pharmaceutical ingredient (API) CDCA, the excipient lactose monohydrate (when needed), the lubricant silica (colloidal anhydrous) and clear hard gelatin capsules. All used starting materials complied to the specifications of the European Pharmacopoeia (Ph.Eur.). CDCA is a white or almost white powder, with molecular formula $C_{24}H_{40}O_4$ and a molecular weight of 392.6 g/mol. The powder is very slightly soluble in water and freely soluble in ethanol (96 per cent), as described in the Ph.Eur. Ph.Eur. reference standards are used in Quality Control. The capsules were packed in pharmaceutical grade HDPE DUMA Twist-Off containers with PP screw caps. All materials were procured from qualified suppliers.

2.2 Pharmacy compounding

Due to bad flowing properties of the CDCA API, 0.5% (w/w) silica was added to the formulation. Depending on CDCA dosage and capsule size, lactose monohydrate was used as a filler substance where needed. The capsules were prepared making a dry powder blend with mortar and pestle, mixing the compounds in equal parts until a homogeneous mixture was created. The powder mixture was manually distributed over the needed amount of capsules using dedicated capsule filling machines, in which a maximum of 100 capsules can be filled simultaneously. Therefore all batch sizes are a multiple of 100 capsules. The following in-process control steps (test that are performed during manufacturing) were incorporated throughout the process: calculation of the weight distribution (RSD) and the deviation from the theoretical weight. This manual production process of pharmacy compounding of capsules is a validated process in the Amsterdam UMC pharmacy, assuring that the capsules are reproducible and consistent.

TABLE 1 Composition of all doses of compounded CDCA capsules and worst-case selection for product validation.

CDCA API (dose)	Silica	Lactose monohydrate	Capsule size	Worst case	Batch size for validation
35 mg	0.5%	Approximately 80%	3	Yes	1,300 capsules
40 mg	0.5%	Approximately 80%	3	No	-
45 mg	0.5%	Approximately 75%	3	No	-
50 mg	0.5%	Approximately 70%	3	No	-
75 mg	0.5%	Approximately 55%	3	No	-
80 mg	0.5%	Approximately 50%	2	No	-
90 mg	0.5%	Approximately 70%	2	No	-
100 mg	0.5%	Approximately 50%	2	No	-
120 mg	0.5%	Approximately 35%	2	No	-
140 mg	0.5%	Absent	2	No	-
200 mg	0.5%	Approximately 30%	0	No	-
250 mg	0.5%	Absent	0	Yes	1,000 capsules

TABLE 2 Product specifications of CDCA capsules according to Ph.Eur.

Test	Specification	Method	References
Appearance	Clear capsule with white or almost white powder	Visual	ICH Q6A, Ph.Eur. 2619
Identity (HPLC)	Positive	Ph. Eur. 2.2.29	ICH Q6A, Ph.Eur. 2619
Related substances (HPLC)		Ph. Eur. 2.2.29	ICH Q6A, Ph.Eur. 2619
-Impurity A (ursodeoxycholic acid)	NMT 1%		
-Impurity B (cholic acid)	NMT 0.5%		
-Impurity C (lithocholic acid)	NMT 0.1%		
-Impurity H (3α,7β-dihydroxy-12-oxo-5β-cholan-24-oic acid)	NMT 0.2%		
-Impurity I (3α-((3α,7α-dihydroxy-24-oxo-5β-cholan-24-yl) oxy)-7α-hydroxy-5β-cholan-24-oic acid)	NMT 0.5%		
-Any other impurity	NMT 0.25%		
-Total impurities	NMT 1.5%		
Assay (HPLC)	90.0%—110.0%	Ph. Eur. 2.2.29	ICH Q6A, Ph.Eur. 2619
Uniformity of dosage units	AV ≤ 15	Ph. Eur. 2.9.40	ICH Q6A, Ph.Eur. 2619, Ph.Eur. 0016
Microbiology			ICH Q6A, Ph.Eur. 2619
-TAMC	NMT 10^3 CFU/g	Ph. Eur. 2.6.12	
-TYMC	NMT 10^2 CFU/g	Ph. Eur. 2.6.12	
-E. Coli	Absent	Ph. Eur. 2.6.13	
Dissolution	≥ 80% at 30 min	Ph. Eur. 2.9.3; medium phosphate buffer pH6.8, assay by HPLC (see assay)	ICH Q6A, Ph.Eur. 0016
-at 5, 10, 15, 20, 30 min			
Disintegration	< 30 min	Ph. Eur. 2.9.1; medium water, with disc	ICH Q6A, Ph.Eur. 0016

TABLE 3 Stability program of CDCA capsules (three 35 mg batches and three 250 mg batches). Long-term conditions are set at 25°C ± 2°C and 60%RH ± 5%RH and accelerated conditions at 40°C ± 2°C and 75%RH ± 5%RH.

		Accelerated		Long-term			
Test	T = 0	T = 3	T = 6	T = 3	T = 6	T = 9	T = 12
Appearance	X	X	X	X	X	X	X
Identity	X	X	X	X	X	X	X
Related substances	X	X	X	X	X	X	X
Assay	X	X	X	X	X	X	X
Uniformity of dosage units	X	-	X	-	X	-	X
Microbiology	X	X	X	X	X	X	X
Dissolution	X	-	X	-	X	-	X
Disintegration	X	-	X	-	X	-	X

2.3 Validation batches

Product validation was performed on predetermined worst-case product doses. Selection factors included were the smallest and largest capsule size, the smallest and largest ratio of lactose monohydrate vs. CDCA API, and the lowest and the highest dose. Based on this, 35 mg CDCA in size 3 capsules and 250 mg CDCA in size 0 capsules were selected as the worst-case products. All doses are summarized in Table 1. The highest dose of 250 mg CDCA with 0.5% silica completely fills the largest capsule size (size 0) and therefore requires no additional lactose. For the lowest dose, 35 mg CDCA API, to fit in the smallest available size 3 capsule, addition of around 80% filler substance lactose monohydrate was needed, which was the highest percentage of lactose of all doses that were being made. For both doses, three validation batches were manufactured, according to European GMP guidelines and national compounding guidelines. During manufacturing, all portions of 100 capsules of a batch were mixed before filling in the containers to assure a homogeneous batch.

2.4 Quality Control

Product specifications were based on the requirements in Ph.Eur. monographs 2619 *Pharmaceutical Preparations* and 0016 *Capsules* and ICH guideline Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and can be found in Table 2 (ICH, 1999). The impurities and acceptance limits were selected based on individual Ph.Eur. monograph 1189 *Chenodeoxycholic Acid*. No additional impurities were expected due to the production process. The high pressure liquid chromatography with differential refractometer (HPLC-RI) analytical method from individual Ph.Eur. monograph 1189 *Chenodeoxycholic Acid* was used.

Additional analytical method validation on specificity and accuracy was performed for identification and quantification of CDCA and its related substances in CDCA capsules. The acceptance criteria for specificity included: all peaks in the chromatograms should be assigned (retention times); in the injection of standard solutions and sample, the active compound CDCA and the specified impurity should be separated with a resolution ≥15%; in the mobile phase no significant peak above reporting threshold should be present which might interfere with CDCA and the known impurity; the retention time of the sample solution CDCA should be between 95%—105% of the retention time of the standard solution. The acceptance criteria for accuracy was a mean recovery of 98%–102% with RSD ≤2%.

2.5 Stability program

The stability program was performed on the validation batches, consisting of three batches of both doses, as required per ICH guideline Q1A (R2) *Stability testing of new drug substances and drug products* (ICH, 2003). The long term stability study at 25°C ± 2°C and 60%RH ±5%RH included testing at time points: 0, 3, 6, 9 and 12 months. The accelerated stability study at 40°C ± 2°C and 75%RH ± 5%RH included testing at time points: 0, 3 and 6 months. At time points 3 and 9 months, reduced testing was performed as not all tests are stability indicating parameters and these were not final time points on which the shelf life would be determined. The tests that were performed at each time point are shown in Table 3.

3 Results

3.1 Product validation

Quality Control results of the product validation show that for both 35 and 250 mg CDCA capsules all six batches complied with the set specifications and therefore complied with Ph.Eur. requirements. All results are shown in Table 4. The products contained the claimed amount of CDCA, with a range of 100.1%–105.5% (specification: 90%–110%). There was little inter-batch variation. The mean assay content of the 35 mg and the 250 mg capsules were 100.8% and 104.7%, respectively. The capsules showed a rapid and reproducible dissolution profile; all batches

10.3389/fphar.2023.1264997

TABLE 4 Results product validation CDCA capsules 35 mg and 250 mg.

Test	Specification	35 mg capsules			250 mg capsules		
		Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
Appearance	Clear capsule with white to broken white powder	Complies	Complies	Complies	Complies	Complies	Complies
Identity (HPLC)	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Related substances (HPLC)							
-Impurity A	NMT 1%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
-Impurity B	NMT 0.5%	<0.05%	<0.05%	<0.05%	<0.05%	<0.05%	<0.05%
-Impurity C	NMT 0.1%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
-Impurity H	NMT 0.2%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
-Impurity I	NMT 0.5%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
-Unspecified impurities	NMT 0.25%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%
-Total impurities	NMT 1.5%	0.0%	0.0%	0.0%	<1.5%	<1.5%	<1.5%
Assay (HPLC)	90.0%—110.0%	100.4%	101.9%	100.1%	104.6%	103.9%	105.5%
Uniformity of dosage units	AV ≤ 15	6	13	10	13.2	9.6	8.8
Microbiology							
-TAMC	NMT 10^3 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g
-TYMC	NMT 10^2 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g	<5 CFU/g
-E. coli	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Dissolution	≥ 80% at 30 min						
–05 min		86.7%	91.8%	76%	74.4%	74.7%	79.9%
–10 min		93.3%	99.8%	98.8%	91.6%	88.5%	94.5%
–15 min		95.9%	101.1%	101.4%	96.1%	99.7%	101%
–20 min		96.4%	101.2%	98.8%	99.6%	102.1%	102.2%
–30 min		94.9%	101%	97.6%	99.3%	103.2%	103%
Disintegration	< 30 min	3 min	2 min	2 min	3 min	3 min	3 min

showed more than 95% dissolution within 15 min and showed little inter-batch variation and variation between the two doses, as shown in Table 4. The test for uniformity of dosage units complied with an acceptance value (AV) ranging from 6 to 13.2 (specification: ≤15), which confirmed that the CDCA API was distributed evenly over the capsules. The capsules had a quick disintegration of ≤3 min (specification: ≤30 min). No degradation products or (microbiological) impurities had formed during the production process. Based on these results, the production process of manufacturing CDCA capsules in a range of 35–250 mg was considered validated.

3.2 Stability studies

Final results, at the end of storage for 6 months on accelerated conditions and 12 months on long-term stability conditions, complied with the preset product specifications. All stability data are shown in Supplementary Tables S1–S4 (Supplementary Table S1: 35 mg capsules accelerated conditions, Supplementary Table S2: 250 mg capsules accelerated conditions, Supplementary Table S3: 35 mg capsules long-term conditions, Supplementary Table S4: 250 mg capsules long-term conditions). Only at the 9 months time-point of the long-term stability study, an out of specification result was found for two of the three 35 mg batches on assay content: 83.8%, 84.1%, and 93.1% (specification: 90%–110%). An investigation was performed but no root cause could be found. Subsequent results at 12 months showed that all results were within specification again. Supplementary Tables S1, S3 show that the assay content of the 35 mg capsules had a high variation, but no simultaneous changes are seen in degradation product. Supplementary Tables S2, S4 show that the assay content of the 250 mg capsules was overall relatively high with an average of approximately 104%, but still within the specification of 90%–110%.

The dissolution of the capsules remained fast during the stability program, the results are shown in Figure 1 and in Supplementary

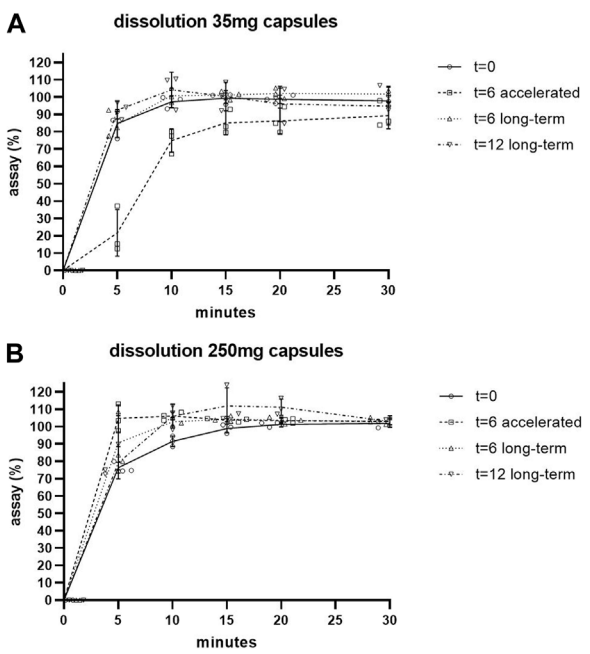

FIGURE 1
Dissolution of 35 mg **(A)** and 250 mg **(B)** capsules during stability studies. Individual values shown. SD shown as error bars.

Tables S1–S4. The specification of ≥80% dissolution within 30 min was reached after 10 min for the 250 mg capsules, both long-term and accelerated conditions, and for the 35 mg capsules long-term conditions (Supplementary Tables S2–S4). For the 35 mg capsules accelerated condition this point was reached after 30 min for all three batches (Supplementary Tables S1). The inter-batch variation that was found in assay could also be seen in the assay percentages that are calculated in the dissolution test, both for the 35 mg and the 250 mg capsules, at all applicable time points in the stability studies.

Other results, as shown in Supplementary Tables S1–S4, showed that related substances had not increased and no unknown impurities had formed. No changes were detected in microbiological results. Uniformity of dosage units and disintegration also remained compliant throughout the stability program.

4 Discussion

From the results of the product validation we conclude that we have developed robust and high quality CDCA capsules in doses suitable for treatment of patients with CTX. The products comply to the set specifications and to national compounding guidelines and EU GMP guidelines. As expected, no impurities arise during the manufacturing process and during stability studies.

The results of the stability studies show that the 250 mg capsules are very stable and therefore a shelf life of 12 months is justified. The results of the 35 mg capsules are less uniform due to the 9 months assay results being below specification. No explanation for this outlier in results could be found. The analytical method has been validated with a high accuracy and an uneven distribution is ruled out as the in process controls show a consistently low RSD based on weight. Future ongoing stability studies are needed to determine if these out of specification results were incidental. Stability issues are not likely as no related substances were increased and no unknown peaks were detected. An analytical error is suspected (for instance in weighing, capsule emptying or sample processing), but could not be confirmed. As we were not able to find a plausible explanation, the shelf life of the 35 mg capsules and all other doses with exception of 250 mg, was set at 6 months.

Overall it can be concluded that the pharmacy compounded CDCA capsules are of high quality and stability. It is often thought that pharmacy preparations are of lower quality compared to commercially manufactured drugs. Using our pharmacy compounded CDCA capsules as an example, we demonstrated that pharmacy compounded drugs are a qualitative and affordable alternative and essential to assure treatment of patients in situations where a commercial drug is unavailable or inaccessible, without compromising on pharmaceutical quality. Furthermore they have an added value in customizing medication dosages to suit individual patients. The Amsterdam UMC pharmacy has supplied more than 60 patients with pharmacy compounded CDCA capsules and around 15% of the patients have received a capsule dose other than 250 mg. For these patients, the personalized compounding of alternative doses is an additional advantage.

This paper offers comprehensive guidance to other pharmacies, enabling them to create high-quality products in a straightforward manner. With this we hope to improve the availability of currently inaccessible drugs through the practice of pharmacy compounding, thereby facilitating improved patient care.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

NB: Formal Analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing–original draft. BJ: Conceptualization, Investigation, Methodology, Supervision, Writing–review and editing. EK: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing–review and editing, Investigation.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Nationale Postcode Loterij, Netherlands.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1264997/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Perspective
PUBLISHED 28 November 2023
DOI 10.3389/fphar.2023.1274532

OPEN ACCESS

EDITED BY
Jean-Marie Boeynaems,
Université Libre de Bruxelles, Belgium

REVIEWED BY
Melania Rivano,
Binaghi Hospital, Italy

*CORRESPONDENCE
Michel M. van den Heuvel,
michel.vandenheuvel@radboudumc.nl

RECEIVED 08 August 2023
ACCEPTED 06 November 2023
PUBLISHED 28 November 2023

CITATION
Buma AIG, Piet B, ter Heine R and van den Heuvel MM (2023), Integrating treatment cost reduction strategies and biomarker research to reduce costs and personalize expensive treatments: an example of a self-funding trial in non-small cell lung cancer.
Front. Pharmacol. 14:1274532.
doi: 10.3389/fphar.2023.1274532

Integrating treatment cost reduction strategies and biomarker research to reduce costs and personalize expensive treatments: an example of a self-funding trial in non-small cell lung cancer

Alessandra I. G. Buma[1], Berber Piet[1], Rob ter Heine[2] and Michel M. van den Heuvel[1]* on behalf of The DEDICATION-1 Consortium

[1]Radboud University Medical Centre, Department of Respiratory Medicine, Nijmegen, Netherlands, [2]Radboud University Medical Centre, Department of Pharmacy, Nijmegen, Netherlands

Personalization of treatment offers the opportunity to treat patients more effectively based on their dominant disease-specific features. The increasing number and types of treatment, and the high costs associated with these treatments, however, demand new approaches that improve patient selection while reducing treatment-associated costs to ensure sustainable healthcare. The DEDICATION-1 trial has been designed to investigate the non-inferiority of lower dosing regimens when compared to standard of care dosing regimens as a potential effective treatment cost reduction strategy to reduce costs of treatment with expensive immune checkpoint inhibitors in non-small cell lung cancer. If non-inferiority is confirmed, lower dosing regimens could be implemented for all therapeutic indications of pembrolizumab. The cost savings obtained within the trial are partly reinvested in biomarker research to improve the personalization of pembrolizumab treatment. The implementation of these biomarkers will potentially lead to additional cost savings by preventing ineffective pembrolizumab exposure, thereby further reducing the financial pressure on healthcare systems. The concepts discussed within this perspective can be applied both to other anticancer agents, as well as to treatments prescribed outside the oncology field.

KEYWORDS

personalized treatment, expensive treatment, treatment cost reduction strategies, sustainable healthcare, biomarker research

1 Introduction

The accumulated body of research and large number of new available treatment options have allowed for a personalization of treatment within multiple therapeutic areas (Zugazagoitia et al., 2016; Schee Genannt Halfmann et al., 2017; Yamamoto et al., 2022). This way, patients can be treated more effectively at the individual patient level based on their dominant disease-specific

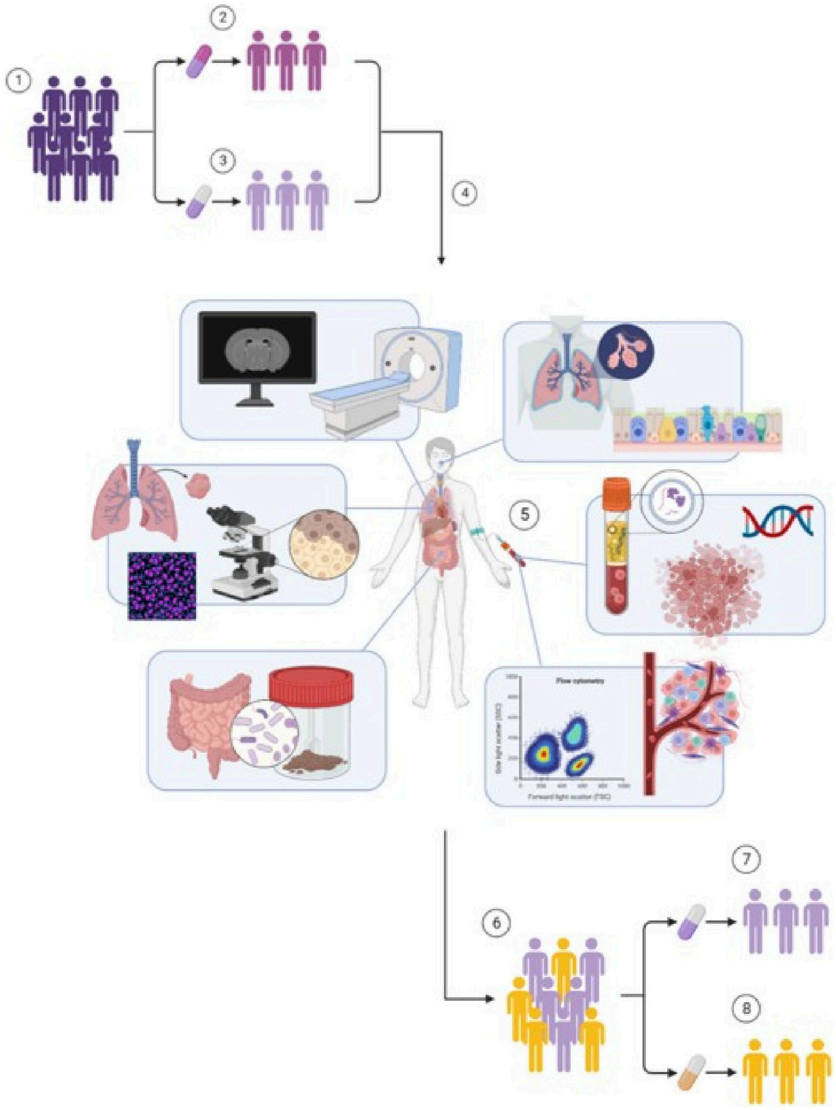

FIGURE 1
Design of the DEDICATION-1 trial. (1) Advanced NSCLC patients without targetable driver mutations eligible for pembrolizumab-containing treatment are randomized in a 1:1 ratio between (2) standard of care regimens and (3) lower dosing regimens of pembrolizumab treatment. (4) Simultaneously, all patients are also included in the biomarker sub-study embedded within the DEDICATION-1 trial. (5) Within this biomarker sub-study, extensive biomarker research is performed that investigates the utility of liquid biopsies, proteomics, pharmacokinetics and immunopharmacology, exhaled breath, AI-based lung imaging, computational pathology, and the microbiome, in predicting (non-)response to pembrolizumab-containing treatment. (6) The implementation of these biomarkers will result in an accurate identification of (7) responders—who will be treated with lower dosing regimens of pembrolizumab treatment if non-inferiority is confirmed—and (8) non-responders—who can receive alternative and possibly more effective treatments –, thereby improving personalization of pembrolizumab-containing treatment and further reducing pembrolizumab exposure and treatment costs in non-responding patients. Abbreviations: NSCLC, non-small cell lung cancer; DEDICATION-1, Dose tapering and Early Discontinuation to InCreAse cosT-effectIveness Of immunotherapy for NSCLC; AI, artificial intelligence.

features (Mathur and Sutton, 2017). Other advantages comprise minimization of overtreatment, avoidance of adverse events, prevention of a delay in administering alternative treatment options, and a potentially marked reduction in overall treatment-associated costs by preventing the administration of ineffective treatment to specific patient subgroups (Jakka and Rossbach, 2013; Cherny et al., 2014; Morkovich, 2023). Two major issues, however, comprise (a) the still limited understanding of the complex underlying biological pathways involved in many diseases, thereby complicating an accurate upfront or early identification of responders to specific treatments, and (b) the high costs of most new treatments (Jakka and Rossbach, 2013; Goetz and Schork, 2018). As a consequence, the sustainability of healthcare systems is increasingly threatened (Jakka and Rossbach, 2013; Goetz and Schork, 2018). New approaches that help improving patient selection while reducing treatment-associated costs in clinical practice are urgently needed (Jakka and Rossbach, 2013; van Ommen-Nijhof et al., 2021; Superchi et al., 2022).

Biomarkers are considered to be essential for the personalization of treatment since they can be used as indicators of pathophysiological processes or pharmacological responses to a

therapeutic intervention (Sarhadi and Armengol, 2022; Morkovich, 2023). Their characteristics make them useful in "providing the right treatment to the right patient, at the right dose, at the right time", thereby preventing unnecessary exposure in patients who do not benefit from a specific treatment. Simultaneously, biomarkers can help obtain valuable insights into the pathophysiological mechanisms underlying the disease of interest (Mishra and Verma, 2010; Landeck et al., 2016). In this perspective, we present an example of a novel, self-funding trial design that integrates both treatment cost reduction strategies and biomarker research to reduce costs and improve personalization of treatment with expensive immune checkpoint inhibitors (ICIs) in advanced non-small cell lung cancer (NSCLC). The concepts discussed within this perspective can be applied both to other anticancer agents, as well as to treatments prescribed outside the oncology field.

2 Overview of the DEDICATION-1 (NVALT 30) trial

In advanced NSCLC patients without targetable driver mutations, different ICIs have been approved and introduced in clinical practice (Twomey and Zhang, 2021). We designed a nationwide multi-center open label randomized non-inferiority trial named "Dose tapering and Early Discontinuation to InCreAse cosT-effectIveness Of immunotherapy for NSCLC" (DEDICATION-1) (NCT04909684) that includes advanced NSCLC patients who are eligible for first-line pembrolizumab-containing treatment in the Netherlands (Figure 1). Pembrolizumab is a fully humanized immunoglobulin G4 monoclonal antibody that is directed against the programmed death-1 (PD-1) receptor, preventing its interaction with programmed death-ligand 1 (PD-L1) and PD-L2, thereby increasing the antitumor immune response (Renner et al., 2019). Based on their tumour PD-L1 expression, patients receive either pembrolizumab monotherapy (PD-L1 expression ≥50%) or pembrolizumab in combination with platinum-based doublet chemotherapy (PD-L1 expression <50%) (Reck et al., 2019; Gadgeel et al., 2020). The primary aim of the trial is to investigate the non-inferiority of a reduced dose *versus* the standard of care dose of pembrolizumab for treatment of advanced stage NSCLC in terms of 1-year overall survival (OS). The secondary aim includes the development of biomarkers predicting (non-)response to pembrolizumab-containing treatment. Currently, 25–30 Dutch sites–both academic and non-academic–are participating in the trial. The following sections will elaborate on the rationale and design of the trial, and the parties involved in the trial.

2.1 Dosing rationale of the DEDICATION-1 (NVALT 30) trial

Dose and schedule selection for ICIs has shown to be challenging since there is no clear dose-response relationship, the toxicity profile of ICIs markedly differs from that of cytotoxic agents, and exposure-toxicity relationships are not yet well understood (Agrawal et al., 2016). Pembrolizumab treatment was initially approved by the US Food and Drug Administration (FDA) in a weight-based dosing schedule of 2 mg/kg every 3 weeks (Q3W) based on results obtained in a phase I trial that investigated pembrolizumab doses up to 10 mg/kg every 2 weeks (Q2W) (Jiang et al., 2022). The trial showed complete peripheral PD-1 target engagement at doses of 1 mg/kg or higher–confirmed by an *ex-vivo* interleukin-2 (IL-2) stimulation test–and no differences in durable anti-tumour activity and dose-limiting toxicities were seen at doses from 1 to 10 mg/kg Q2W (Renner et al., 2019; Low et al., 2021; Hirsch et al., 2022). In addition, no differences in response rates between doses of 2 mg/kg Q3W and higher were observed in the subsequent expansion cohorts, implying that increasing pembrolizumab dose from 2 mg/kg to higher does not contribute to tumour control (Low et al., 2021; Hirsch et al., 2022). Since doses lower than 2 mg/kg were not examined, it remains unknown whether systemic exposure associated with doses lower than 2 mg/kg Q3W results in sufficient intratumoral PD-1 inhibition and, therefore, in effective treatment (Li et al., 2021; Low et al., 2021).

To enhance convenience and reduce spill of partially used vials, pembrolizumab treatment was later also approved in a fixed dosing schedule of 200 mg Q3W or a high-dose, extended-interval dosing schedule of 400 mg every 6 weeks (Q6W) based on results obtained in *in silico* investigations (Freshwater et al., 2017; Jiang et al., 2022). Note that these investigations showed that a fixed dose of 150 mg Q3W–and not 200 mg Q3W–resulted in pharmacokinetically equivalent exposure as the initially approved dose of 2 mg/kg Q3W (Freshwater et al., 2017). With ever increasing restrictions on healthcare budgets and the high costs associated with pembrolizumab treatment, a re-evaluation of the current dosing regimens has often been suggested (Jiang et al., 2022).

The DEDICATION-1 (NVALT 30) trial has been designed to investigate whether treatment with lower dosing regimens is non-inferior to treatment with standard of care dosing regimens. Advanced NSCLC patients eligible for pembrolizumab-containing treatment are randomized in a 1:1 ratio between standard of care and lower dosing regimens of pembrolizumab treatment (Figure 1). The standard of care dosing regimens comprise the currently registered 400 mg Q6W dosing regimen and a 150 mg Q3W dosing regimen. The lower dosing regimens consist of a 300 mg Q6W and a 100 mg Q3W dosing regimen. Note that the 150 mg Q3W and 100 mg Q3W dosing regimens can be considered pharmacokinetically equivalent to the 400 mg Q6W and 300 mg Q3W dosing regimens, respectively, based on simulated trough plasma concentration (C_{trough}) levels (Figure 2). Since PD-1 inhibition directly correlates with pembrolizumab concentration and the concentration level is lowest just before the next administered dose, it is hypothesized that the C_{trough} level is the most informative pharmacological parameter to predict treatment efficacy (Li et al., 2021). Hence, no difference in efficacy is expected between the pharmacokinetically equivalent dosing regimens investigated within the trial.

Pembrolizumab is currently commercially available in 4 mL vials, corresponding to a 100 mg dose per vial (each ml of concentrate contains 25 mg of pembrolizumab) (European Medicines Agency, 2015). This would result in only partially used vials for each patient if the lower dosing regimen of 300 mg Q6W would be applied. In 2020, however, employees of Merck published an article on the physiochemical stability of pembrolizumab

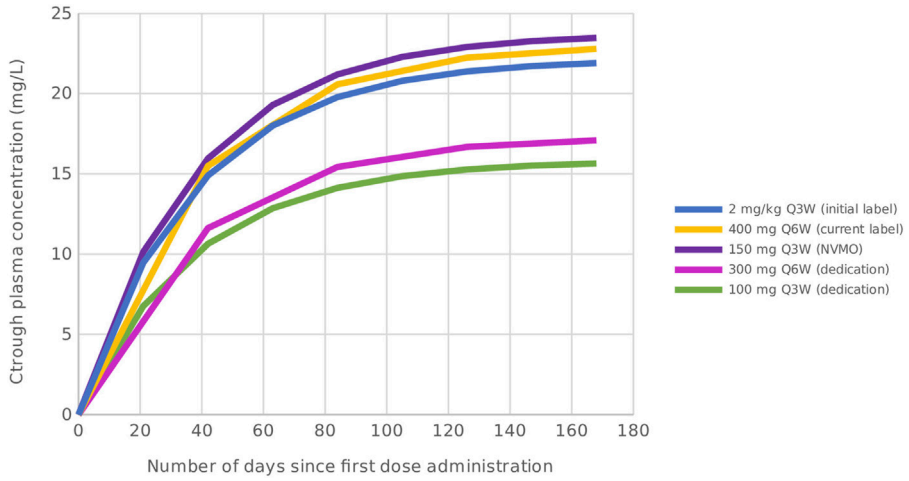

FIGURE 2
Simulated C_{trough} levels of pembrolizumab for the initially approved dosing regimen, and the standard of care and lower dosing regimens investigated within the DEDICATION-1 trial. Based on the simulated C_{trough} levels, the 150 mg Q3W and 100 mg Q3W dosing regimens can be considered pharmacokinetically equivalent to the 400 mg Q6W and 300 mg Q3W dosing regimens, respectively. Abbreviations: C_{trough}, trough plasma concentration; Q3W, every 3 weeks; Q6W, every 6 weeks; NVMO, Nederlandse Vereniging voor Medische Oncologie; DEDICATION-1, Dose tapering and Early Discontinuation to InCreAse cosT-effectIveness Of immunotherapy for NSCLC.

admixture solution (25). Results showed that pembrolizumab has a longer shelf-life than currently stated in the package leaflet, if adequate aseptic conditions can be maintained during reconstitution (Sundaramurthi et al., 2020). This enables the use of a single vial for multiple patients, thereby preventing unnecessary costs due to spill of only partially used vials when applying the lower dosing regimens.

2.2 Design and sample size calculation of the DEDICATION-1 (NVALT 30) trial

According to the US FDA guidance on pharmacokinetic-based criteria for supporting alternative dosing regimens of PD-1 and PD-L1 inhibitors, lower dosing regimens cannot be considered pharmacokinetically equivalent to the standard of care dosing regimens if they are expected to result in more than 20% lower exposure (U.S. Department of Health and Human Services, 2022). Additional clinical data to support efficacy of the proposed lower dosing regimens are then considered necessary (U.S. Department of Health and Human Services, 2022). In line with the practical recommendations on the level of evidence needed to apply alternative dosing regimens in clinical practice published by *Overbeek et al.*, we selected a prospective non-inferiority design to provide high quality evidence for lower dosing of pembrolizumab treatment (Overbeek et al., 2023).

Based on the European Medicines Agency (EMA) guidelines for performing non-inferiority trials, the lower dosing regimens can only be defined non-inferior to the standard of care dosing regimens if the following two criteria are simultaneously met: (a) The efficacy of the lower dosing regimens is allowed to be worse than the standard of care dosing regimens if the difference is within a pre-specified clinically relevant boundary, and (b) the lower dosing regimens must still be superior to the treatment used as control in the trials that led to registration of the standard of care dosing regimens (Committee for medical products for human use CHMP, 2005). In our trial, non-inferiority is confirmed if (a) with 95% one-sided confidence the absolute difference in 1-year OS rate is below 10%, and (b) with 95% two-sided confidence the 1-year OS in the lower dosing regimens arm is superior to that of a virtual cohort of patients receiving chemotherapy. The 1-year OS rate in the virtual cohort of patients receiving chemotherapy will be estimated based on the KEYNOTE-024 and KEYNOTE-189 studies with a ratio between patients with a tumour PD-L1 expression <50% and ≥50% equal to that observed in our trial (Committee for medical products for human use CHMP, 2005).

Based on the abovementioned criteria, the inclusion of 750 patients who are followed for at least 1 year is needed to yield (a) 90% power to declare non-inferiority according to the first criterion–assuming an equal true 1-year OS rate on both treatment regimens of 70%–and (b) 91% power to find non-inferiority when the percentage of patients with a tumour PD-L1 expression ≥50% is lower than 75% according to the second criterion. The power of the trial will drop in case the percentage of patients with a tumour PD-L1 expression ≥50% is higher than the estimated 75%, or if the true 1-year OS rate is lower than the estimated 70%. The worst case–still assuming an equal 1-year OS rate in both arms–would appear if the true survival rate is 50%. This would yield a power of 86% to declare non-inferiority.

An interim analysis will be performed after the first 250 patients have been included and followed for at least 1 year. Inclusion in the trial will be stopped early if among these patients a difference of 10% or higher in 1-year OS rate is observed in favour of the standard of care dosing regimens. Patients already included in the trial at that time point will still be followed until 1 year after inclusion for the final analysis. The stopping boundary of 10% corresponds to a conditional power of 5%. This is relatively low when compared to the conditional

power of 15%–which corresponds to a stopping boundary of 8%–usually applied for futility analyses. However, we considered a stopping boundary of at least 10% to be clinically relevant. An early stopping rule for efficacy is not considered to be necessary since we do not expect the lower dosing regimens to be superior to the standard of care dosing regimens.

2.3 Biomarker research and development within the DEDICATION-1 (NVALT 30) trial

Pembrolizumab-containing treatment is currently prescribed as a non-personalized first-line treatment, since it has been approved for all advanced NSCLC patients who lack targetable driver mutations regardless of their tumour PD-L1 expression (Reck et al., 2019; Gadgeel et al., 2020). In clinical practice, however, only half of these patients experience a clinical benefit (Grizzi et al., 2017; Reck et al., 2019). As a result, a large proportion of patients is unnecessarily exposed to potential treatment-related adverse events, and will not receive alternative–and potentially more effective–treatment options for this rapidly progressing disease (Cherny et al., 2014; Morkovich, 2023). The cost savings obtained by investigating pembrolizumab dose reduction are, therefore, not only being used to fund the clinical trial itself, but also to fund the biomarker sub-study that is embedded within the DEDICATION-1 trial to improve personalization of pembrolizumab treatment through accurate patient selection (Figure 1).

Due to the complexity of the mechanism of action of ICIs and the many factors that influence a patient's likelihood to response, it is expected that more than one biomarker will be needed to improve patient selection and clinical decision making (Blank et al., 2016). Therefore, the DEDICATION-1 trial has been designed to serve as a platform for extensive biomarker research that investigates multiple biomarkers (e.g., liquid biopsies, proteomics, pharmacokinetics and immunopharmacology, exhaled breath, artificial intelligence (AI)-based lung imaging, computational pathology, and the microbiome) in order to assess their utility–both individually and within the context of a compound biomarker–in predicting (non-)response to pembrolizumab-containing treatment. Importantly, the trial design allows for the development of predictive biomarkers that are able to identify both primary treatment resistance (e.g., predictive biomarkers that predict (non-)response before start or early after start of treatment) and secondary treatment resistance (e.g., monitoring biomarkers that can be applied to identify (non-) response during course of treatment) (Buma et al., 2021; van Delft et al., 2022; Buma et al., 2023). In parallel, an early Health Technology Assessment (HTA) analysis is being performed to assess the value of biomarker-guided treatment selection by providing high-quality research information on the effectiveness, costs, and impact of the implementation of such an approach (Ferraro et al., 2022). This way, the investigated biomarkers not only provide valuable new insights on the pathophysiological mechanisms underlying advanced NSCLC disease and the pharmacological behaviour of ICI agents, but simultaneously have a high chance of being actually implemented in clinical practice to guide appropriate prescription of pembrolizumab-containing treatment, and facilitate patient education and counseling.

3 Self-funding–a double edged sword to improve sustainable healthcare by public parties

In current practice, new drugs are being developed by pharmaceutical companies alongside with companion diagnostics if available. As soon as the drug has entered the market, the need for further optimization and personalization of treatment is often hampered by the commercial interests of these companies. There is no intrinsic motivation other than increasing or continuing their market share. However, healthcare providers and other public parties, responsible for creating an affordable and sustainable healthcare system, do feel the motivation to further fine tune the treatment.

The DEDICATION-1 trial is a unique joint-venture of public parties who pursue affordable and sustainable healthcare. The parties include (a) healthcare professionals, who are directly involved in clinical care or management of patients, (b) healthcare insurers, who are essential in providing access to the alternative dosing regimens, and (c) the patient advocate organization Longkanker Nederland, who meets the needs of the lung cancer patients for which the alternative dosing regimen has been proposed. The trial is additionally supported by the Dutch healthcare professional associations Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT) and Nederlandse Vereniging van ZiekenhuisApothekers (NVZA). Collaboration between these public parties and national healthcare associations is crucial to structurally perform trials like the DEDICATION-1 and to increase adherence if cost-effective dosing regimens are implemented in clinical practice. External funding of the trial is provided by the Treatmeds foundation, which is an initiative of the Dutch healthcare insurers and aims to keep expensive treatments affordable and available, by financially supporting approaches that reduce high treatment costs while maintaining treatment efficacy.

4 Discussion

The increasing number and types of available treatment options, and the high costs of these new treatments, demand new approaches that improve patient selection while reducing treatment-associated costs to ensure sustainable healthcare (Jakka and Rossbach, 2013; van Ommen-Nijhof et al., 2021; Superchi et al., 2022; van Till et al., 2022). Within the DEDICATION-1 trial, we apply lower dosing of pembrolizumab as a potential effective strategy to reduce pembrolizumab treatment-associated costs. The cost savings are partly reinvested in biomarker research in order to improve the personalization of treatment through an upfront or early identification of patients who might benefit from it. The implementation of these biomarkers will potentially lead to additional cost reductions due to prevention of ineffective pembrolizumab exposure, thereby further reducing the financial pressure on healthcare systems.

Pembrolizumab is currently prescribed for many different solid malignancies (Stewart, 2021). Based on data obtained in nivolumab, which also targets PD-1, one could argue that higher doses of anti-PD-1 treatment are required to achieve optimal

efficacy in NSCLC when compared to other malignancies (Agrawal et al., 2016). This would imply that lower dosing regimens could also be implemented for all therapeutic indications without compromising efficacy if non-inferiority in NSCLC is confirmed (Renner et al., 2019; Jiang et al., 2022). This would substantially decrease the significant costs associated with global pembrolizumab prescription. On the other hand, we expect that biomarkers do vary for the different therapeutic indications. Each cancer type is characterized by unique molecular and histopathological features (Hoadley et al., 2014; Komura et al., 2022). This may result in distinct features associated with (non-) response to pembrolizumab-containing treatment, thus requiring different (combinations of) predictive or monitoring biomarkers. For instance, a different set of serum tumour markers is valuable for monitoring treatment response in NSCLC when compared to breast or colorectal cancer (Duffy, 2006; Jelski and Mroczko, 2020). Consequently, the application of a prediction model developed for identifying (non-)response in NSCLC will need to be adapted for other cancer types. The cost savings obtained through the universal application of lower pembrolizumab dosing could be used to develop cancer type-specific biomarkers that improve personalization of pembrolizumab-containing treatment in cancers other than NSCLC.

The integration of treatment cost reduction strategies and biomarker research can also be applied to improve personalization of other treatments even outside the oncology field. Different strategies have already shown to be effective for cost reduction of several anticancer agents (Serritella et al., 2020). Abiraterone, for example, is an enzyme inhibitor indicated for prostate cancer which has a large food effect (Ratain, 2011). Results obtained within a randomized non-inferiority trial showed abiraterone administration at 250 mg with a low-fat meal to be non-inferior in clinical endpoints and pharmacodynamic effects when compared to standard of care administration at 1,000 mg while fasting (Szmulewitz et al., 2018). Another example is the application of shorter adjuvant treatment duration in breast cancer patients who can be treated with six instead of 12 months of adjuvant trastuzumab, and in colon cancer patients in whom 3 months of adjuvant chemotherapy was shown to be as effective as 6 months (Grothey et al., 2018; Earl et al., 2019). Note that in the current era of personalized medicine, the drugs in these examples–and most of other currently available treatments–are still prescribed applying a one-size-fits-all approach as for pembrolizumab-containing treatment. Cost reduction strategies could therefore not only be used to reduce financial pressure on healthcare systems, but also to improve the personalization of a high number of treatments by funding the development and implementation of companion biomarkers that guide treatment selection and therapeutic monitoring in clinical practice. In addition, the increased knowledge gained on the pathophysiological mechanisms underlying the disease of interest could possibly help develop new and more effective treatment options.

The DEDICATION-1 trial is also an example of a framework that can be adopted to effectively reduce current treatment costs and improve personalization of treatments in the short-term. However, one could argue that the concept of the DEDICATION-1 trial is simply a direct consequence of our current healthcare price setting and regulation system. Whether the implementation of this framework will thus be effective on the long-term, is unknown. Until sustainable solutions for drug pricing and healthcare reimbursement are implemented, trials like the DEDICATION-1 can be performed to develop lower-cost and personalized treatment regimens (Uyl-de Groot and Löwenberg, 2018).

In conclusion, we presented the DEDICATION-1 trial as an example of a novel, self-funding trial design that integrates both treatment cost reduction strategies and biomarker research to reduce costs and improve personalization of treatment with expensive ICIs in advanced non-small cell lung cancer (NSCLC). The concepts discussed within this perspective can be applied both to other anticancer agents, as well as to treatments prescribed in other therapeutic areas in order to improve their personalization and cost-effectiveness in the short-term.

The DEDICATION-1 Consortium

Paul Brinkman, Anke H. Maitland-van der Zee (Department of Respiratory Medicine, Amsterdam University Medical Centre); Daan van den Broek, Huub van Rossum (Department of Laboratory Medicine, Netherlands Cancer Institute); Sjaak Burgers (Department of Respiratory Medicine, Netherlands Cancer Institute); Francesco Ciompi, Katrien Grünberg (Department of Pathology, Radboud University Medical Center); Simona M. Cristescu (Institute for Molecules and Materials, Radboud University); Bram van Ginneken, Colin Jacobs (Diagnostic Image Analysis Group, Radboud University Medical Center); Lizza Hendriks (Department of Respiratory Medicine, Maastricht University Medical Center); Jeroen Hiltermann (Department of Respiratory Medicine, University Medical Center Groningen); Firdaus Mohamed Housein (Department of Radiology, University Medical Center Utrecht); Alwin Huitema (Department of Pharmacy and Pharmacology, Netherlands Cancer Institute); Jakko van Inge (Department of Medical Microbiology, Radboud University Medical Center); Hans Koenen, Ruben Smeets (Department of Laboratory Medicine, Radboud University Medical Center); Marjolijn Ligtenberg (Department of Tumor Genetics, Radboud University Medical Center); Vincent van der Noort (Department of Statistics, Netherlands Cancer Institute); Mathias Prokop (Department of Radiology and Nuclear Medicine, Radboud University Medical Center); Heinrich Roder (Biodesix); Valesca Rètel (Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute); Thomas Würdinger (Department of Neurosurgery, Amsterdam University Medical Center and Free University Medical Center).

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

AB: Conceptualization, Visualization, Writing–original draft. BP: Conceptualization, Writing–review and editing. RH: Conceptualization, Supervision, Writing–review and editing. MH: Conceptualization, Supervision, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The DEDICATION-1 trial is conducted with funding of Stichting Treatmeds. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 28 November 2023
DOI 10.3389/fphar.2023.1199500

OPEN ACCESS

EDITED BY
Atse Huisman,
Health Insurers Netherlands, Netherlands

REVIEWED BY
Giovanni Migliaccio,
Consorzio per Valutazioni Biologiche e Farmacologiche, Italy
Patricia Vella Bonanno,
University of Malta, Malta
Sinaa Al Aqeel,
King Saud University, Saudi Arabia
Caridad Pontes,
Autonomous University of Barcelona, Spain

*CORRESPONDENCE
Juan Carlos Rejon-Parrilla,
juancarlos.rejon@juntadeandalucia.es

RECEIVED 03 April 2023
ACCEPTED 06 November 2023
PUBLISHED 28 November 2023

CITATION
Rejon-Parrilla JC, Espin J, Garner S, Kniazkov S and Epstein D (2023), Pricing and reimbursement mechanisms for advanced therapy medicinal products in 20 countries.
Front. Pharmacol. 14:1199500.
doi: 10.3389/fphar.2023.1199500

Pricing and reimbursement mechanisms for advanced therapy medicinal products in 20 countries

Juan Carlos Rejon-Parrilla[1]*, Jaime Espin[2,3,4,5], Sarah Garner[6], Stanislav Kniazkov[6] and David Epstein[7]

[1]Health Technology Assessment Area (AETSA), Andalusian Public Foundation Progress and Health (FPS), Seville, Spain, [2]Andalusian School of Public Health, Granada, Spain, [3]Instituto de Investigación Biosanitaria ibs, Granada, Spain, [4]CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain, [5]Cátedra de Economía de la Salud y Dirección de Organizaciones Sanitarias (Esalud2), Granada, Spain, [6]World Health Organization Regional Office for Europe, Copenhagen, Denmark, [7]Department of Applied Economics, University of Granada, Granada, Spain

Introduction: Advanced Therapy Medicinal Products are a type of therapies that, in some cases, hold great potential for patients without an effective current therapeutic approach but they also present multiple challenges to payers. While there are many theoretical papers on pricing and reimbursement (P&R) options, original empirical research is very scarce. This paper aims to provide a comprehensive international review of regulatory and P&R decisions taken for all ATMPs with centralized European marketing authorization in March 2022.

Methods: A survey was distributed in July 2022 to representatives of 46 countries.

Results: Responses were received from 20 countries out of 46 (43.5%). 14 countries reimbursed at least one ATMP. Six countries in this survey reimbursed no ATMPs.

Conclusion: Access to ATMPs is uneven across the countries included in this study. This arises from regulatory differences, commercial decisions by marketing authorization holders, and the divergent assessment processes and criteria applied by payers. Moving towards greater equality of access will require cooperation between countries and stakeholders, for example, through the WHO Regional Office for Europe's Access to Novel Medicines Platform.

KEYWORDS

advanced therapy medicinal products (ATMPs), pricing and reimbursement (P&R), pharmaceutical policy, survey, health technology assessment (HTA)

1 Introduction

Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that are based on genes, tissues or cells (EMA, 2022a). Some of these therapies hold great potential for patients without an effective current therapeutic approach (Hanna et al., 2016; Lamas-Díaz and Hernández-García, 2020). Development is rapid in this area. By October 2022, 19 ATMPs had received full, conditional or exceptional marketing authorization (MA) in the European Union (EU) (Aguilera-Cobos et al., 2022). The Food and Drugs Administration (FDA) forecasts that by 2025 they will approve every year between 10 and 20 cell and gene therapies (Food and Administration, 2019). However, the

individual companies choose whether to submit products for regulation, to the FDA or to other regulatory bodies in other regions, as well as for registration and reimbursement in particular countries. For example, whilst a product may have a central marketing authorization, the companies can then decide when and where to launch or file for reimbursement.

The generation of evidence in therapeutic areas where there is an unmet medical need can be challenging (Vreman et al., 2019). The PRIority MEdicines (PRIME) scheme was developed by the European Medicines Agency (EMA) to enhance technical support for the development of medicines that target an unmet medical need. Many ATMPs target unmet needs. Almost half (45%) of PRIME designations (Aguilera-Cobos et al., 2022)–combining medicines that were once granted PRIME designation but that are no longer in the scheme and therapies that are in the scheme at the time of writing–were ATMPs (EMA, 2022c) (Supplementary Annex S1). Furthermore, ATMPs, up to now, have almost all been designated as orphan drugs for rare diseases (14 out of the 19 approved by the EMA).

In order to facilitate early access for patients, where a product addresses an unmet need, regulators can give a conditional MA on the basis of early data, providing certain conditions are met including the provision of further evidence (Bloem et al., 2023). However, this often means that MA holders then file for reimbursement with insufficient evidence to support the claim of cost-effectiveness (Bloem et al., 2023), particularly in the long-term. As these medicines are often priced highly this creates high financial and clinical uncertainty and risk for payers. Outcomes-based (or pay-for-performance (P4P)) arrangements offer instruments that can mitigate financial risk, limit the patient population and generate further evidence. Qualitative research suggests that some experts view P4P schemes as potential enablers for MA holders to meet many of their strategic goals (Wenzl and Chapman, 2019). Early access allows sales to be initiated sooner in the product life cycle, allowing earlier returns on capital.

Whilst regulatory policies are being adopted in Europe to facilitate the accelerated approval of ATMPs (Fürst-Ladani et al., 2023), the complexities of the existing pathways are often seen as a barrier by therapy developers (Pizevska et al., 2022). However, if marketing authorization is successfully obtained, gaining access to a market where there was previously unmet need can set up the product as the market leader, develop economies of scale, and potentially establish it as the new standard of care ("first-mover advantage"). Furthermore, sales can be made without changing the "official" price of the product in that country (i.e., the net price of a therapy in a country does not need to be the same as its list price (Dubois, 2019)), which is advantageous for the MA holder in countries that adopt external reference pricing. Whilst that can be attractive to manufacturers, it can raise questions about equity in access (Kanavos et al., 2020).

The way ATMPs are administered has relevance for decision making both from clinical and reimbursement perspectives. Unlike most medicines, which can be withdrawn if no response is achieved, gene therapies are one-off treatments. Out of the 15 indications (13 ATMPs) in our sample, 14 are intended for single administration (Supplementary Annex S1). Due to the early and often sparse evidence base at launch, the clinical and economic data that reaches Health Technology Assessment (HTA) and reimbursement stage can be insufficient for healthcare systems to assess their added therapeutic value with certainty (Angelis et al., 2020; Lloyd-Williams and Hughes, 2021) and to negotiate value-based prices (Hanna et al., 2018). The difficulty of demonstrating value to payers, very small fragmented markets, and manufacturing and logistical difficulties have been cited as reasons for the withdrawal of some ATMPs from the market in Europe (Aguilera-Cobos et al., 2022).

Payers handling the difficult task of managing financial risk and uncertain evidence, where it exists, need to embed risk management strategies into their pricing and reimbursement (P&R) decision making processes, and they often do so through special pricing mechanisms (Hanna et al., 2018; Gonçalves, 2021; Jørgensen and Kefalas, 2021). While there are many theoretical papers on P&R options (Carr and Bradshaw, 2016; Godman et al., 2018; Gonçalves, 2021; Ádám et al., 2022), original empirical research is very scarce. The Organization for Economic Co-operation and Development (OECD) conducted a survey of experts on the use of managed entry agreements (MEA) in 12 countries (Wenzl and Chapman, 2019) but did not deal with specific therapies. A few papers describe country experiences of P&R arrangements (Jørgensen et al., 2020; Facey et al., 2021; Jørgensen and Kefalas, 2021; Ronco et al., 2021). This paper aims to provide a comprehensive international review of regulatory and P&R decisions taken for all ATMPs with European marketing approval in March 2022. We consider regulatory approval, reimbursement status, use of special P&R arrangements (type and aims) and arrangements for further evidence collection and re-assessments.

2 Methods

A survey was distributed in July 2022 to 46 countries (see Supplementary Annex S2) through the Pharmaceutical Pricing and Reimbursement Information (PPRI) Network, a unique collaboration of pharmaceutical P&R authorities with 50 members from national competent bodies (mostly European) and international institutions. The PPRI enables members to exchange information and data on P&R decisions and policies (Vogler et al., 2015; GOG, 2022).

By March 2022, 13 ATMP had received European central MA via the EMA. 2 of them have 2 licensed indications with European central MA (Supplementary Annex S1), making for a total of 15 therapy-indication pairs. All were included in our survey.

Data collection sheets were pre-filled with information from the literature review or previous PPRI Network enquiries where available. Respondents were allowed approximately 3 weeks to respond, with one reminder, and were contacted again to clarify responses that were unclear. The survey included questions about the regulatory approval status in the country (not all operated through the European centralized MA procedure), reimbursement status, the reasons for not reimbursing in case the ATMP is not reimbursed, whether any special arrangements are in place to finance the therapy (such as coverage with evidence development, discounts or rebates–see Supplementary Annex S3 for definitions), the main purpose of special arrangements (for example, control expenditure, share risk), whether information on the scheme is publicly available, how further evidence is to be collected (if any),

whether reassessment of the evidence, coverage or price is planned, and any other further information respondents may want to provide. The survey and responses were all in English (the questions asked in the survey are transcribed in Supplementary Annex S4). We reviewed targeted peer reviewed and grey literature to contrast the answers to our survey, and to contextualize them. A draft of this manuscript was circulated amongst responders to ensure we captured their responses accurately. Our focus was on national policies. Within some countries, the manufacturer can negotiate contracts with individual social health insurance bodies, regional health authorities, hospitals, or the private healthcare sector, including P4P schemes. We indicate the cases where our respondent had knowledge of these decentralized agreements, but there may be other similar cases which we were not informed about. We provide a narrative description of results for each country, and consider common themes and suggest policy recommendations in the discussion. The data are anonymized in accordance with the World Health Organization's (WHO) Framework for Engagement with non-State actors so as not to confer any endorsement of a specific non-State actor's name, brand or product.

3 Results

Responses were received from 20 countries out of 46 (43.5%) (Supplementary Annex S2). 6 of those countries (Armenia, Australia, Brazil, Canada, Israel and Türkiye) do not operate through the European MA procedure (See Supplementary Annex S5). Differences in regulatory status in these countries compared to the EMA, for the ATMPs under study, were observed in 44 instances. The regulatory status in Türkiye, where none of the ATMPs had received regulatory approval at the time of the survey (see Supplementary Table S1 and Supplementary Annex S5 for further details), showed the starkest difference compared to their status with regards to the European centralized regulatory system. Armenia, Brazil, Bulgaria, Iceland, Malta and Türkiye did not reimburse any ATMP (Supplementary Table S1). Malta and Iceland do operate through the European centralized regulatory system, but had not received applications for reimbursement for any ATMPs. To overcome this situation, the government of Malta has an agreement for hematology patients in need of an ATMP to be treated in the United Kingdom. In Brazil, ATMP12 is under assessment and pending a reimbursement decision, for ATMP5 the price has been appealed and ATMP7 was rejected for reimbursement based on the budget impact. Bulgaria, supporting their decision by HTAs in some cases, decided not to fund any of the ATMPs in the list. Armenia gave no reasons for the lack of reimbursement for all ATMPs included in our study, hence we excluded this country from Supplementary Table S1.

14 countries reimbursed at least one ATMP (Supplementary Table S2). Austria and Israel provided no information about P&R schemes. ATMP13 was withdrawn by the manufacturer from Europe. Hence, we did not include it in Supplementary Table S2.

4 of the ATMPs included in our study were chimeric antigen receptors (CAR) T-cells medicines (CAR-Ts) (ATMPs 1, 5, 10 and 11). Previous research in a smaller sample of countries (Germany, Italy, Spain, France and United Kingdom) and ATMPs (11 included, of which 2 were CAR-Ts) found that the CAR-Ts they included in their study were being reimbursed in the countries they observed (Ronco et al., 2021). Our results show wide variation in access across countries for CAR-Ts, with ATMP1 being reimbursed in 2 countries (France and Germany), ATMP5 [indication 5 (I5)] in 13 countries, ATMP5 (indication 6) in 11 countries, ATMP 10 in 4 countries (Israel, France, Germany and Italy), ATMP11 (both for I12 and I13) in the same 11 countries. We observed no systematic differences in reimbursement status (Supplementary Table S1) or P&R arrangement used for reimbursement (Supplementary Table S2) between CAR-Ts and other types of ATMPs.

3.1 Australia

In Australia, the purpose of all special arrangements used to finance ATMPs was to share risks. These agreements were always associated to the collection of further evidence. The Pharmaceutical Benefits Advisory Committee (PBAC) does provide advice on the nature of the patient registry that is most suitable in each case (i.e., a disease-based one or therapy-based ones), as well as the minimum data to be collected. For instance, for both indications of ATMP11 and ATMP5, they recommend the Australian Bone Marrow Transplant Recipient Registry, for ATMP7 they recommended including data from Australian patients in the Novartis international registry, and for ATMP12 they noted that a disease-based registry would be suitable, instead of therapy-based registries. For all therapies the manufacturer would be responsible for providing any new data to the HTA committee, which would re-assess the new evidence. The periods for reassessment varied between 2 years from commencement of public financing for both indications of ATMP11 and ATMP5, 3 years for ATMP7 and 5 years for ATMP12.

The special pricing and reimbursement arrangements used for ATMPs were confidential. However, the PBAC does publish its recommendation. For ATMP11, ATMP7 and ATMP12, the PBAC recommended a P4P risk sharing arrangement combined with a confidential discount. For ATMP5, they recommended a P4P.

3.2 Canada

In Canada the regulatory authority (Health Products and Food Branch (HPFB) of Health Canada) can issue a Notice of Compliance (NOC), which corresponds to an MA, or a NOC with conditions, corresponding to a Conditional MA. Special agreements to finance medicines are confidential. They may involve simple discounts (e.g., first dollar rebates), incremental rebates in the event an annual threshold is exceeded, and other forms of risk-sharing arrangements. There are special arrangements in place for all 3 ATMPs being reimbursed (ATMP5, ATMP11 and ATMP12). Whether the agreements are linked to the collection of further evidence is also confidential. For therapies that are indeed being subject to the collection of further evidence as part of managed access schemes, such evidence would be meant to inform the clinical and cost-effectiveness parameters of a reassessment (HTA). The institutions responsible for the collection and analysis of this further evidence are the pan-Canadian Pharmaceutical Alliance (pCPA) and/or provincial

and territorial drug plans. In Canada, any drug that is reimbursed in the public healthcare system could be eligible for a proactive or reactive reassessment (CADTH, 2022).

3.3 Israel

Israel applies special pricing and reimbursement agreements for both indications of both ATMP11 and ATMP5, ATMP2, ATMP7, ATMP10 and ATMP12. However, information about the arrangements is either confidential, not publicly available or not known to the respondents of our survey. In all cases, the schemes are subjects of the collection of further evidence, which is to be collected and analyzed by the Ministry of Health of Israel, although no further information about this is publicly available.

3.4 Czechia

In the Czechia, the national HTA body only makes assessments of drugs for outpatient settings. ATMP2 and ATMP3 have been recommended in this context. ATMP2 is subject to a special confidential reimbursement arrangement to control expenditure. ATMP3 is reimbursed without any special arrangement. The HTA body does not assess therapies for in-hospital settings, and have no record of their use. Reimbursement in the hospital settings is theoretically possible for all products within the scope of our study and lies within the competency of health insurance companies and hospitals.

3.5 Denmark

Denmark reimburses 4 ATMPs: ATMP3, ATMP7, ATMP12 and ATMP5 (only its indication for B-cell acute lymphoblastic leukemia). ATMP7 is financed by a P4P model in yearly instalments conditioned on continuing clinical response, with data collected by the national procurement agency and healthcare providers (Amgros, 2020). The main aim was to control expenditure.

3.6 France

France reimburses most ATMPs (Supplementary Table S1), with confidential price discounts. The information about whether or not the reimbursement arrangements include mandatory evidence collection is confidential. If such data collection was mandated, the responsibility for collecting this information would fall under the Technical Agency for Information on Hospitalization (AITH), and the health ministry would be responsible for analyzing the data. Health technology re-assessment of ATMP11 (both indications), ATMP5 (both indications) and ATMP10 are planned for mid-2023, and in 2024 for ATMP2 and ATMP7. In each case the price can be revised during the entire life cycle of the product. If the HTA assessment indicates that the therapy provides major added clinical value, France has a system to inject additional funding to cover the costs of ATMPs administered in hospitals, on top of the existing diagnosis related group (DRG) fee (Ronco et al., 2021). Eligibility for inclusion in this "add-on list" is based on the cost of the product compared with the tariff applied to the DRG (cost>30% of the tariff). As a result, for ATMP5 and ATMP11, an additional 15,000€ was added in France on top of the DRG fee (Ronco et al., 2021). ATMP3 and ATMP1 were assessed as providing minor added clinical value and no added clinical value respectively, compared with existing alternatives, and so hospitals can use these therapies but receive no additional DRG-funding from the national health insurance system for doing so.

3.7 Germany

All ATMPs in this study were being reimbursed in Germany (Schaefer et al., 2021), except for 2 (i.e., ATMP9 and ATMP13), which had been taken off the market by the company (Qiu et al., 2022). In the German market, all new therapies used to be reimbursed at a price freely set by the company during the first year, after which manufacturers negotiate the price of their product with the social insurance providers (Epstein and Espín, 2020). In November 2022, a policy reform (namely, the GKV-Finanzstabilisierungsgesetz or SHI Financial Stabilization Act) shortened the period of free pricing to 6 months (Kleining et al., 2023). In a regular benefit assessment, a drug would only be able to command a premium price if the evidence established a "major" or "substantial" added benefit. The law makes an exception for orphan drugs. Added benefit is "assumed" for orphan drugs as soon as they get European central MA if the total expenditure is less than €50 million per year (Schaefer et al., 2021). Hence in these cases the drugs are reimbursed at premium prices. This has proved controversial (IQWiG, 2022) and concerns have been raised about the spill-over effect on the prices of orphan drugs throughout international markets, since prices of medicines in Germany weigh heavily in the baskets used to estimate reference prices in other countries (Kanavos et al., 2017; Gill et al., 2019). Diverse local MEAs and P4P schemes have been negotiated between the manufacturer and local payers in Germany (Europe, 2019). At the end of 2019 routine practice data collection was required binding the manufacturer to set up a patient registry and to submit results yearly (Benazet et al., 2020; Senior, 2021). In Germany, there are no special arrangements at national level to finance ATMPs (as stated in Supplementary Table S2), but social health insurers negotiate outcomes-based rebates with manufacturers (Jørgensen and Kefalas, 2021; Ronco et al., 2021).

3.8 Greece

Greece applies confidential special arrangements to finance ATMP11 (indications 12 and 13) and ATMP5 (indications 5 and 6), ATMP12 and ATMP7. The main aim of the special arrangements is to control expenditure. For ATMP11 and ATMP5 there is a budget cap (there may be additional, confidential, components), with additional data collection over 2 years, followed by a planned reassessment and renegotiation.

3.9 Italy

At the time of writing, Italy had decided to reimburse 8 of the ATMPs included in our study, for 10 different indications. To reimburse them, Italy uses a range of types of P&R arrangements (see Supplementary Table S2). Most of the arrangements in place to finance ATMPs in Italy are P4P payment models, paid in instalments (upon result), linked to individual patient data, and applying a confidential discount. Although the size of the discount is kept confidential, information about the P&R arrangement applied is made publicly available in Italy. ATMP7 is reimbursed applying a budget cap, and outcomes are followed through the Italian regulator's (AIFA) registry (linking prescriptions and payments/rebates to clinical outcomes (Jørgensen et al., 2019)). For ATMP10 and ATMP6, the arrangement is similar but a simple discount was applied instead of a budget cap.

All ATMPs reimbursed in Italy are subject to the collection of further evidence collected by AIFA registries. The technological architecture of the registries is resourced by companies but governed by AIFA (Xoxi et al., 2021). This evidence is subsequently used to reassess the value of the therapy, which usually occurs after 2 years from the agreement signature or in case of extension of indication. Some of these ATMPs were assigned the so called AIFA innovativeness recognition (i.e., ATMP3, ATMP7, ATMP10, ATMP6 and ATMP12), which entitles them to being financed in Italy through a special innovative drug fund, plus becoming immediately available in regional formularies, and exempt from the usual pay-back mechanism (Fortinguerra et al., 2020).

3.10 Netherlands (Kingdom of the)

The special arrangements to finance ATMPs are confidential in nature, but in general terms, they were implemented to improve cost-effectiveness and to control expenditures. Only 2 of the special arrangements in place to finance ATMPs in the Netherlands (Kingdom of the) were organized centrally by the government (ATMP7 and ATMP12). The rest were arranged by insurance providers. ATMP11 was re-evaluated based on 3-year survival data and budget impact, which resulted in a confidential discount of the price of at least 5%. Netherlands (Kingdom of the) is also a member of the BENELUXA Initiative, which recently published an HTA jointly produced between the Netherlands (Kingdom of the), Ireland and Belgium for ATMP6 (Policy, 2022), resulting in a recommendation not to reimburse unless cost effectiveness can be improved relative to existing treatment. The countries that constitute the initiative have not yet entered in joint negotiations to reach reimbursement terms for this product (Policy, 2022).

3.11 Slovenia

Slovenia applies special arrangements for the reimbursement of ATMP5 (indication 5 and 6), ATMP2 and ATMP12. The main purpose of these financing schemes is to control expenditures, and they achieved this through confidential discounts. None of these schemes are associated with the collection of further evidence.

3.12 Spain

In Spain, the special arrangements to finance ATMPs aimed to share risk and to control expenditure. In most cases this comprised a P4P scheme, combined with restrictions in the eligible patient populations. ATMP7 and ATMP12 were financed with P4P schemes combined with expenditure cap and a price-volume agreement respectively. All of them involved the collection of further evidence, which was in all cases operationalized through a national registry operated by the health ministry (Sistema de Información para determinar el VALor TERapéutico de MEDicamentos, which stands for Information System to determine the Therapeutic Value of Medicines, or VALTERMED) (Jørgensen et al., 2020). VALTERMED's data collection protocols are made publicly available at the website of the Spanish Ministry of Health (both in Spanish and in English). Each decentralized region in Spain has a monitoring committee responsible for data collection and quality. Data analysis and re-assessment will be conducted by the health ministry "when sufficient data become available", and some provisional data have been published (Sanidad, 2022).

3.13 Sweden

In Sweden, the county councils are responsible for in-patient care, which includes ATMPs. A committee called the New Therapies Council supports county councils, enabling the equality of the system. Also, upon request of the regions, the national HTA agency can perform an assessment of the health economic evidence. This level of fragmentation makes it difficult to access information about what financing schemes are in place in Sweden for ATMPs and how they are operationalized. Nevertheless, county councils do publish information about which therapies have a managed entry agreement in place, and the dates associated with reassessment.

Considering the above, although limited in scope, we do have some information about the reimbursement status of ATMPs in Sweden and how it has been operationalized. ATMP11 (indications 12 and 13), ATMP5 (indication 5 only) and ATMP12 are financed through special arrangements. For ATMP11 (indications 12 and 13), a rebate may be required conditional on further evidence collection through the European Society for Blood and Marrow Transplantation (EBMT) patient register and quality local registers. The same registry is used to collect further evidence for ATMP5, but there is no further detail available around the financing arrangement. For ATMP12, the agreement consists of a confidential discount, and the collection of further evidence, operationalized through the national quality register for neuromuscular diseases (NMiS). ATMP7 is the only ATMP reimbursed in Sweden for which there is no public report of a special financing arrangement being in place.

4 Discussion

Six countries in this survey reimbursed no ATMPs due to a variety of reasons, including regulatory and reimbursement decisions made by the regulators, the payers or the companies themselves (see Supplementary Table S1 for further details). Where a particular ATMP was financed, there was considerable variability across countries in the types of P&R arrangements used (see

Supplementary Table S2 for further details). For instance, ATMP5 and ATMP11 were reimbursed using at least 6 different formulas comprising combinations of P4P, discounts, expenditure caps and restrictions on the patient population. No countries used subscription models or more exotic financial instruments (models and instruments that are further described in Supplementary Annex S3 and discussed in the academic literature (Vogler, 2022b)).

There was considerable variation in the type of P4P schemes for ATMPs in our sample. We identified areas where examples of best practice can be helpful for schemes to achieve their objectives. These included the provision of clear objectives, sharing of information between different departments of the health system, availability of information about the parameters of the agreement (or even whether one exists), and clarity about when, how or by whom the data will be analyzed and re-assessed. Improvement in these areas is a prerequisite that enables the necessary alignment between key stakeholders, including industry and health system actors, for these kinds of schemes to successfully fulfil their purpose, but the necessary human resources and expertise needs to be invested by all involved parties into reaching excellence and productive cross-stakeholder collaboration (Dunlop et al., 2018).

P4P databases in our sample were usually set up using either existing disease registries or purpose-build stand-alone platforms. None of the responses received indicated that routine healthcare administrative databases were used. This may be because, for example, such platforms do not collect the appropriate diagnosis, treatment or outcome variables. The new regulation on European cooperation on HTA does not have any provision for collaboration on post-launch evidence generation (PLEG) (Puñal-Riobóo et al., 2022). This would have enabled the development of common protocols and standards (Iorio et al., 2018; COMET, 2022). The requirement for busy clinicians to manually input (or re-input) P4P data in stand-alone platforms can mean that data is often omitted or duplicated (Ferrario et al., 2017; Godman et al., 2018; Hanna et al., 2018; Michelsen et al., 2020; Facey et al., 2021; Jørgensen and Kefalas, 2021). European cooperation on this area should not only be limited to the actual collection of data, but also on developing capacity in countries, and a further understanding and guiding countries around the methods to quantify the costs and the benefits of risk-sharing, and of the implementation of the different types of schemes available to articulate it (Towse and Garrison, 2010).

At a European level, data sharing across jurisdictions may be essential to leverage the benefits of further evidence generation, especially for ultra-rare diseases (Facey et al., 2021). The role of the European Commission in incentivizing or enforcing the collection of further evidence after conditional centralized marketing authorizations are granted is controversial. Furthermore, research has raised concerns about the delays in the delivery and flaws in the design of post-marketing studies under these schemes, both in Europe and the United States (Salcher-Konrad et al., 2020). The EU has initiated a flagship program to share reports and analyses of regulatory healthcare data (Data Analysis and Real-World Interrogation Network, DARWIN) (Facey et al., 2020). However, perhaps the absence of a central European HTA process and payment mechanism explains that no similar EU-wide initiative addresses the sharing of data that might help address uncertainties at this level, which is a national competency. Furthermore, national governments are responsible for primary data quality. Databases require financial investment (Jørgensen and Kefalas, 2019) and the expertise and leadership to make sure the data is relevant and of sufficient quality (Vogler, 2022b). P4P arrangements can be associated with increased burden to those administering them, while rebates, discounts, price caps and price-volume arrangements can be managed with relatively straightforward contracts and routine administrative healthcare information systems (Hanna et al., 2018). The research undertaken for this paper indicates that there is scope for further European collaboration exploring strategies for countries to build capacity to administer and/or share the burden of the more complex P&R options and increase transparency.

At a country level, the United Kingdom (England) created the Innovative Medicines Fund to ensure fast, provisional access to promising but uncertain treatments, particularly ATMPs, while further evidence is generated (Anderson et al., 2022) and control over budget impact is maintained. The aim of this fund is to provide the system with a route to provide access to selected therapies deemed particularly promising whilst facilitating the collection of further evidence likely to mitigate initial decision uncertainties to avoid the potential opportunity costs associated with these costly therapies (Angelis et al., 2023). The fine details around how this fund is operationalized, particularly around (but not limited to) providing finer definitions of entry requirements such as what is considered to be a promising treatment, or what is deemed to be a 'step-change in treatment', and other operational aspects such as what provisions will be put in place for therapies that fail to prove their added value and/or being appropriate use of limited public resources, will determine its success (Angelis et al., 2023). Other countries, such as Italy (Masini et al., 2021) and Canada (Chan et al., 2020; Dai et al., 2021), have developed similar frameworks. Dedicated funds such as these are intended to prevent innovative but uncertain high-cost medicines from displacing other cost-effective interventions while further evidence is generated. However, these siloed funds fragment the pharmaceutical budget and need to be carefully managed and combined with other policies to ensure spending in pharmaceuticals remain affordable and efficient (Mills and Kanavos, 2020). An alternative approach is applied in Australia, where the PBAC has recommended existing disease registries for P4P monitoring. The advantage in principle of disease registries over intervention registries is the potential to estimate comparative effectiveness, subject to appropriate adjustment for confounding by indication (Hatswell et al., 2020). Countries without a defined strategy to fund and manage the collection of further evidence in the context of managed entry agreements might tend to seek simpler P&R agreements with MA holders (such as straight discounts), not because that is the most suitable option to meet their needs in a given P&R decision, but for practicality.

In the sample of responses received, information about the price or the P&R arrangement used to fund a therapy tended to be confidential in nature. While a degree of confidentiality can facilitate negotiation (Joosse et al., 2022), ethically there is a case for enabling reporting of clinical evidence that is accrued using public money under the access schemes (Dal-Ré, 2015; Guerra-Júnior et al., 2017). The World Health Assembly Resolution 72.8 calls for more transparency across a number of areas including prices in other countries, costs of research and patent expiry (Perehudoff, 2022). More transparency across these areas, including MEA schemes, would facilitate P&R decisions and potentially improve access for patients (Commission, 2020; Vogler, 2022a; Webb et al., 2022).

There appears to be considerable variation across regulatory body outcomes. For example, Türkiye has not approved any ATMP

and other regulatory bodies have yet to assess all the products. The individual companies choose whether to submit products for regulation and registration in particular countries. For example, whilst a product may have a central European authorization the companies can then decide when and where to launch or file for reimbursement. Our survey shows that the variability of access is in part due to choices made by regulatory and reimbursement authorities, and in part due to commercial decisions by companies about regulatory and reimbursement submissions.

The new European regulation on HTA will help shape the a landscape for ATMPs in the EU, since it stipulates that from 2025 onwards, ATMPs will be required to undergo joint clinical assessments, with the potential of significantly mitigating current differences between national comparative effectiveness assessments (Julian et al., 2022; Angelillo et al., 2023). However, launching and filing for reimbursement and funding decisions will remain at a national level so the overall impact is difficult to assess at this stage. Furthermore, an additional factor that can lead to fragmentation of the EU market is related to the complex manufacturing, logistics and clinical protocols that commercial ATMPs can require (Aguilera-Cobos et al., 2022) and the threat for these costs, or others like the need to translate packaging into each member's official language, to make smaller countries less commercially attractive for manufacturers, particularly for rare diseases.

The results of our study highlight considerable variation in the approaches used by individual countries to provide access to ATMPs and the scope for voluntary collaborations to overcome some of the existing barriers, particularly for smaller countries. For example, some of the options available to them include joint P&R negotiations for new medicines for demand pooling (to increase the volume), collaboration on the administration of ATMPs (through joint treatment centers), or cross-country collaboration on real-world-evidence generation (Angelillo et al., 2023). There are a number of good examples of collaboration in the European region: FINOSE (Finland, Norway, Sweden), BENELUXA or the Valletta Declaration, or bilateral arrangements such as those between Malta and the United Kingdom (i.e., Malta has an agreement for hematology patients in need of an ATMP to be treated in the United Kingdom, as presented at the beginning of the results section).

The development of detailed treatment protocols (including all associated costs), and clear communication of it to stakeholders, would facilitate cross-border collaboration enabling international multidisciplinary care teams to build on existing infrastructures such as the European Reference Networks (ERNs) to deliver care and to collect evidence, which would provide a European instrument to collaborate towards mitigating uncertainties (Angelillo et al., 2023). The view of patient representatives is that, although pooled procurement of ATMPs has not yet been extensively explored, it should be considered more widely (Benvenuti et al., 2021). Options suggested to boost cross-border collaboration in Europe to enhance access to ATMPs include innovative solutions that are yet to be tried, such as providing care through regional expert treatment centers (Angelillo et al., 2023).

As the evidence we present in this paper shows, many products are not submitted for reimbursement in individual countries with priority being given to larger markets. Members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) have committed to "file for pricing and reimbursement in all EU countries as soon as possible and no later than 2 years from the central EU market authorization, provided that local systems allow it" (Associations, 2022). The Pharmaceutical Strategy for Europe notes that many developers of ATMPs benefit from financial or other incentives during the development phases and the EC is exploring "conditionality" of those push incentives to support broader access and increase competition (Commission, 2020). However these proposals have sparked significant debate and reactions from stakeholders, including representatives of the Commission (Gallina, 2023), hospital pharmacists representatives (Kohl, 2021), the European pharmaceutical industry (Associations, 2020) and academic researchers (Garattini et al., 2021) amongst others. There is considerable variation in ability to pay across the European Region. Therefore, in order to support equitable access across smaller and lower income countries, more explicit consideration of pricing principles will be required, ensuring that any use of external reference pricing is appropriate and mechanisms to preventing arbitrage are in place (Docteur, 2022).

Our survey has only included "commercial" ATMPs, developed by private MA holders. There are also now several so-called "academic" ATMPs (Egea-Guerrero et al., 2019; Juan et al., 2021; Trias et al., 2022), developed by non-profits (EMA, 2022b) or public-private collaborations (Priesner and Hildebrandt, 2022) under hospital exemption regulations (Coppens et al., 2020; Trias et al., 2022). In some cases the manufacturer is preparing for centralized MA (EMA, 2022b). The potential role of academic ATMPs has been highlighted as a potential route to creating a generic market for this kind of therapies, however multiple barriers prevent this from happening (Seoane-Vazquez et al., 2019). It remains to be seen how regulation, pricing and competitiveness of academic ATMPs will compare with commercial ones (Cuende et al., 2014; Seoane-Vazquez et al., 2019).

4.1 Strengths and limitations of this study

This paper has described the P&R landscape in 2022 for 15 ATMPs in 20 countries, a much larger sample of products and countries than other articles (Jørgensen et al., 2020; Jørgensen and Kefalas, 2021; Ronco et al., 2021). There may of course be other arrangements in other countries. The countries were mainly high-income, with two upper middle-income. More research is needed on P&R arrangements in low- and middle-income countries (Castro et al., 2019), and in smaller countries too (focusing for instance in the countries included in the WHO led Small Countries Initiative–a network of 11 European countries with 2 million or less inhabitants, out of which 3 were included in our survey). The survey was in English, which was not the first language of most respondents. We attempted to clarify and classify common terms with respondents across diverse language and institutional settings. The survey was directed at national authorities for P&R. To greater or lesser extent, decision making may be decentralized, as in Sweden, Germany and Spain.

5 Conclusions and recommendations

In this section, and in Supplementary Table S3, we have summarized the key areas for further development and the recommendations associated to each.

The work undertaken has demonstrated that there is wide variation in access to ATMPs between the countries surveyed. Furthermore, that this variation has a number of reasons

including regulatory differences, commercial decisions by MA holders, and the divergent assessment processes and criteria applied by payers. Moving towards greater equality of access will require cooperation between countries and stakeholders, together with relevant international actors such as the WHO Regional Office for Europe's Access to Novel Medicines Platform.

There is also considerable cross-country variation in how P4P schemes are used for a particular ATMPs. This imposes transaction costs on healthcare systems and MA holders, and limits opportunity for data sharing. In line with WHA 72.8, greater transparency, particularly where public funding has been used, will enable dialogue about the schemes in use, and the development of common protocols, terminology and standards for data collection, will lower costs and generate better quality evidence, ultimately with benefits for patients.

The inclusion of post-launch evidence generation in the new European regulation on cooperation in HTA could formalize arrangements. A specific proposal along these lines was made by EURORDIS, which suggested the co-creation, with multi-stakeholder input, of a data strategy for the European Reference Networks (ERNs) to progress towards the common implementation of a European data infrastructure, building on the existing infrastructure of the Networks (EURORDIS, 2020).

Demand pooling and pooled procurement of ATMPs has not yet been frequently used, should be considered more widely (Benvenuti et al., 2021) and could facilitate evaluation, evidence generation, pricing and ultimately access in all countries due to the stronger negotiating position they would acquire, but particularly in small countries (Angelillo et al., 2023).

There have been several examples of non-profit development of "academic" ATMPs. Careful evaluation of these initiatives should be undertaken, considering the legal and regulatory framework, accounting methods for estimating costs, incentives, P&R pathways for these kinds of products and the implications for competition with commercial medicines.

In the mid-term, more investment in enhancing HTA and (other) infrastructures to support P&R processes (be it through a strong European HTA infrastructure supporting the new regulation, and/or enhancing resources deployed nationally), accompanied by coordinated efforts to further develop the necessary expertise, would highly benefit decision makers dealing with complex P&R decisions for ATMPs.

Data availability statement

The datasets presented in this article are not readily available because The data are anonymized in accordance with the World Health Organization's (WHO) framework for engagement with non-State actors so as not to confer any endorsement of a specific non-State actor's name, brand or product. Requests to access the datasets should be directed to SG, garners@who.int.

Author contributions

JR-P played a leading role in the design of this study, analysis, and the interpretation of the results as well as in the write-up of this paper, participated in the collection of the data and wrote the first draft of the manuscript. DE, JE, and SG participated in the design, data collection and analysis, and in the interpretation of the results. SK played a leading role in the collection of the data and participated in the design of the study. All authors contributed to the article and approved the submitted version.

Funding

This study has received support from research project PID 2019.105597RA.I00 financed by the Spanish Ministry of Science and Innovation/National Research Agency MCIN/AEI/10.13039/501100011033.

Acknowledgments

The authors acknowledge the support of the Pharmaceutical Pricing and Reimbursement (PPRI) network whose members provided data for this research. The PPRI network is an informal collaboration of competent pharmaceutical pricing and reimbursement authorities of 50 mostly European countries as well as European and international institutions. The aim of this network is to facilitate information exchange on pharmaceutical policy issues between public officials, supported by scientific evidence. The authors are also grateful to the PPRI Secretariat affiliated to the Pharmacoeconomics Department at Gesundheit Österreich GmbH (Austrian National Public Health Institute) for granting access to the network. The views expressed in the publication are those of the authors.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1199500/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 29 January 2024
DOI 10.3389/fphar.2023.1265029

OPEN ACCESS

EDITED BY
Atse Huisman,
Health Insurers Netherlands, Netherlands

REVIEWED BY
Simon Paul Jenkins,
University of Warwick, United Kingdom
Dario Sacchini,
Catholic University of the Sacred Heart, Italy
Luis Laranjeira,
Eli Lilly, Portugal

*CORRESPONDENCE
Charlotte H. C. Bomhof,
c.bomhof@erasmusmc.nl

RECEIVED 21 July 2023
ACCEPTED 29 December 2023
PUBLISHED 29 January 2024

CITATION
Bomhof CHC, Smids J, Sybesma S, Schermer M and Bunnik EM (2024), Ethics of access to newly approved expensive medical treatments: multi-stakeholder dialogues in a publicly funded healthcare system.
Front. Pharmacol. 14:1265029.
doi: 10.3389/fphar.2023.1265029

Ethics of access to newly approved expensive medical treatments: multi-stakeholder dialogues in a publicly funded healthcare system

Charlotte H. C. Bomhof*, Jilles Smids, Sybren Sybesma, Maartje Schermer and Eline M. Bunnik

Department of Medical Ethics, Philosophy and History of Medicine, Erasmus MC, Rotterdam, Netherlands

Background: Due to rising healthcare expenditures, countries with publicly funded healthcare systems face challenges when providing newly approved expensive anti-cancer treatments to all eligible patients. In the Netherlands in 2015, the so-called Coverage Lock (CL), was introduced to help safeguard the sustainability of the healthcare system. Since then, newly approved treatments are no longer automatically reimbursed. Previous work has shown that as policies for access to CL treatments are lacking, patient access to non-reimbursed treatments is limited and variable, which raises ethical issues. The ethics of access were discussed in a series of multi-stakeholder dialogues in the Netherlands.

Methods: Three dialogues were held in early 2023 and included physicians, health insurers, hospital executives, policymakers, patients, citizens, and representatives of pharmaceutical companies, patient and professional organizations. In advance, participants had received an 'argument scheme' featuring three models: 1) access based on third-party payment (e.g., by pharmaceutical companies, health insurers or hospitals) 2) access based on out-of-pocket payments by patients 3) no access to CL treatments. During the dialogues, participants were asked to discuss the merits of the ethical arguments for and against these models together, and ultimately to weigh them. The discussions were audio-taped, transcribed, coded, and thematically analyzed.

Results: Generally, most stakeholders were in favour of allowing access–at least when treatments are clearly beneficial–to treatments in the CL. When discussing third-party payment, stakeholders favoured payment by pharmaceutical companies over payment by health insurers or hospitals, not wanting to usurp collective funds while cost-effectiveness assessments are still pending. Largely, stakeholders were not in favour of out-of-pocket payments, emphasizing solidarity and equal access as important pillars of the Dutch healthcare system. Recurrent themes included the conflict between individual and collective interests, shifting attitudes, withholding access as a means to put pressure on the system, and the importance of transparency about access to CL-treatments.

Conclusion: Policies for access to non-reimbursed treatments should address stakeholders' concerns regarding transparency, equal access and solidarity, and loss of potential health benefits for patients. Multi-stakeholder dialogues are an important tool to help inform policy-making on access to newly approved (too) expensive treatments in countries facing challenges to the sustainability of healthcare systems.

KEYWORDS

empirical bioethics, stakeholder engagement, access to expensive treatments, healthcare policy, ethics

1 Introduction

Due to rising healthcare expenditures and a proliferation of expensive medical treatments, countries with publicly funded healthcare systems face challenges when providing newly approved expensive anti-cancer treatments to all eligible patients. As healthcare budgets are limited, increasing use of expensive treatments can lead to the crowding out of other types of healthcare (Rekenkamer, 2020). To safeguard the financial sustainability of healthcare systems, countries apply a range of policies (Stadhouders et al., 2019). As an example of a policy aimed at containing the cost of new expensive treatments, last year, Germany changed the law to reduce the period in which new treatments are reimbursed at the list price from twelve to 6 months. Thus, the price that is negotiated on the basis of health technology assessment will (retroactively) apply after six instead of 12 months, which saves costs (Koyncu, 2022). In the Netherlands in 2015, the so-called Coverage Lock (CL) was introduced to safeguard a sustainable healthcare system (Kleijne, 2016). Since then, newly approved expensive treatments entering the market are no longer automatically reimbursed (see Box 1), which delays patient access to these treatments. Until now, the ethical implications of CL have not been systematically evaluated. In this study, the ethics of access to treatments placed in the CL were discussed in a series of multi-stakeholder dialogues in the Netherlands. As stakeholder engagement is essential for responsible development and implementation of policies (OECD, 2021), more insight into stakeholders' perspectives regarding access to non-reimbursed treatments is urgently needed, especially in countries with publicly funded healthcare systems.

Box 1 The healthcare system and Coverage Lock in the Netherlands

The Netherlands is a country with a publicly funded healthcare system, based on solidarity, granting comprehensive healthcare for all patients (Zorginstituut Nederland, 2022). In practice, this means that all citizens have a mandatory health insurance, which provides them access to all medically necessary care that is reimbursed within the basic healthcare package. Some treatments which are newly approved by the European Medicines Agency (EMA) are not immediately reimbursed within the basic healthcare package, but first placed in the CL (Zorginstituut Nederland, 2020). A treatment is placed in the lock if it has a budget impact exceeding 20 million euros a year for all patients with the disease for which it is prescribed, or if it costs 50,000 euros or more per patient with total costs exceeding

(Continued in next column)

Box 1 (*Continued*) The healthcare system and Coverage Lock in the Netherlands

a budget impact of 10 million euros a year for one disease. While treatments are in the CL, the Dutch Healthcare Institute issues an advice whether to include the treatment in the basic healthcare package–based on the four criteria efficacy, cost-effectiveness, feasibility and necessity–and when necessary, the Dutch Ministry of Health, Welfare and Sports negotiates with the pharmaceutical company regarding the price. Since the instalment of the CL in 2015, 57 treatment indications have been assessed in the lock (Zorginstituut Nederland, 2023). In July 2023, the Ministry of Health, Welfare and Sports lowered the threshold of the total budget impact of treatments to enter the CL from 40 to 20 million euros (Kuipers, 2023), which means that from July 2023 onwards, an increasing number of newly approved treatments will be placed in the CL. In 2021 and 2022, treatments spent–on average–510 days in the CL (Vereniging Innovatieve Geneesmiddelen, 2023). Most treatments that come out of the CL are included in the basic healthcare package at undisclosed prices. In March 2023, however, for the first time since the introduction of the CL in 2015, negotiations were unsuccessful: Trodelvy, a third-line treatment for triple-negative breast cancer which gives approximately 5.4 months life-prolongation and costs 68,707 euros per patient per treatment, was not included in the basic healthcare package. The Dutch Healthcare Institute recommended inclusion into the basic healthcare package only if the pharmaceutical company would agree to a price reduction of 75%, which the pharmaceutical company did not (Rijksoverheid, 2023b). Also Libmeldy, a treatment for the rare genetic disorder Metachromatic Leukodystrophy, was not included in the basic healthcare package after unsuccessful price negotiations (Rijksoverheid, 2023a). Currently, there are no policies in the Netherlands regarding access to CL treatments, and it is unclear whether patients are able to access treatments that are not (yet) included in the basic healthcare package.

While treatments are in the CL, health insurers have no obligation to reimburse them. Pharmaceutical companies are allowed–but likewise, not obliged–to provide the treatments to patients free of charge through managed access programs. In the period 2015–2020, many pharmaceutical companies did provide managed access to treatments in the CL (Barjesteh van Waalwijk van Doorn-Khosrovani et al., 2021). However, it is unclear for how many patients or in how many hospitals access was possible. A previous interview study amongst a diverse group of Dutch stakeholders regarding access to Nusinersen while it was in the lock, showed that stakeholders perceived the time which treatments spent in the lock to be too long (Scheijmans et al., 2022). Another interview study amongst Dutch physicians showed that physicians sometimes encounter problems when they want to prescribe treatments which are in

the CL (Bomhof et al., 2022). This study also showed differences in physicians' practices: while some physicians tried to arrange access to non-reimbursed treatments for patients, for instance by asking the hospital to fund the treatment, apply for leniency by insurance companies, or look for managed access programs, other physicians did not, because it would take too much time, would involve a lot of administrative work, or because they expected that their application would not be granted. Therefore, it seems that patient access to treatments which are in the CL is sometimes limited and variable in the Netherlands. This raises ethical questions regarding equal access to CL-treatments. As it is expected that the number of CL-treatments will increase in the near future, the need for policies safeguarding fair access to CL-treatments is becoming more urgent.

In this paper, we report on the methods and results of a series of multi-stakeholder dialogues we conducted, which included physicians, health insurers, hospital executives, policymakers, patients, citizens, and representatives of pharmaceutical companies, patient organizations and professional organizations, regarding three policy options or 'models' for access to treatments in the CL: 1) access based on third-party payment (e.g., by pharmaceutical companies, health insurers or hospitals) 2) access based on out-of-pocket payments by patients 3) no access to non-reimbursed treatments. These 'models' are descriptions of the various possible access routes. Depending on how these access models are (morally) evaluated, the need may arise to design policies to regulate them. That is, access routes may simply be allowed, or on the contrary, be disincentivized or prohibited altogether. Alternatively, they may be not merely allowed, but actively regulated in order to enhance transparency and promote equal access. In advance, we had developed an argument scheme featuring an overview of the moral arguments for and against allowing these three access models. The aim of our study was twofold. Firstly, we aimed to validate and further develop the argument scheme–aimed to aid policymakers and other stakeholders when designing policy options for ethical access to non-reimbursed treatments–through discussion with a diverse group of stakeholders. And secondly, we aimed to bring together groups of stakeholders with different perspectives, who normally would not discuss the ethics of access together, to facilitate the exchanging of ideas and perspectives, stimulate stakeholders to weigh ethical arguments against each other, and search for common ground. Interaction between stakeholders with varying perspectives is important when discussing policy, as it can bring new arguments to the fore, help deepen a discussion, and make sure all relevant impacts are weighed (OECD, 2021). Ultimately, multi-stakeholder discussions can thus help find common ground and advance the societal discussion on fair access to non-reimbursed medical treatments.

Although this study was performed within the Dutch healthcare system, its results are also relevant for other countries with publicly funded healthcare systems. As governments are grappling with problems concerning limited healthcare budgets and increasingly expensive treatments that could potentially crowd out other types of healthcare, insight into stakeholders' perspectives regarding the ethics of access to non-reimbursed treatments is highly relevant for all countries with publicly funded healthcare systems.

2 Materials and methods

2.1 Methodological approach

This study was part of the last phase of a broader empirical bioethics research project regarding the ethics of access to non-reimbursed treatments. In empirical bioethics research projects, roughly 3 phases are distinguished: the phase of *mapping* of the field (for instance with a literature study), the phase of *framing* of the research problem or area (further exploring a specific problem or area, for example, by conducting qualitative interviews) and the phase of *shaping* of the terrain (for instance, by developing normative recommendations for new policies) (Huxtable and Ives, 2019). This study was part of the third phase of our research project, and aims to integrate the empirical work with the normative. Therefore, it does not remain only descriptive of individual stakeholder perspectives, but in bringing varying stakeholders together to exchange different moral perspectives and weigh ethical arguments, it seeks common ground and tries to develop recommendations. There are roughly two kinds of overarching approaches in integrating the empirical and normative work within empirical bioethics: the consultative approach and the dialogical approach (Davies et al., 2015). In the consultative approach, the normative analysis takes place after stakeholders are consulted. The input from stakeholders is collected and analyzed afterwards by the researcher, and normative conclusions are developed after the interaction has taken place–often after consulting ethical theories. In the dialogical approach, normative claims are developed during the interaction with stakeholders, often seeking a shared understanding or consensus (Widdershoven et al., 2009; Davies et al., 2015). In previous studies, we have used the consultative approach, and conducted qualitative interview studies to understand stakeholders' perspectives (framings) on the ethics of access (Bomhof et al., 2022). As diverse groups of stakeholders are affected by this dilemma, and policies should ideally be supported by these groups of stakeholders, for this study, we have chosen a dialogical approach aimed at shaping the terrain. As methodologies used for integrated empirical bioethics are diverse and often remain inexplicit, researchers within empirical bioethics have been called upon to reflect upon the normative justification and methodological approach used (Davies et al., 2015). With these dialogues, we aim to contribute to the tradition of the dialogical approach, by developing a format in which stakeholders *with diverse backgrounds* could exchange perspectives and weigh moral arguments together, potentially leading to normative common ground or recommendations.

2.2 Design of dialogues

Three in-person multi-stakeholder dialogues were held in two meeting centres in Utrecht, a central location in the Netherlands, in February and March 2023. Each stakeholder dialogue included seven to eight purposively selected participants. The meeting rooms had a hollow-square set-up to facilitate interaction between participants. At the start of the dialogues, agreements were made regarding

confidentiality and respectful dialogue to create a safe environment. All dialogues were led by the same moderator (MS). Other members of the research team (EB, CB, JS, SS) were also present to take notes, to ask questions for clarification or follow-up, or to answer factual questions from participants. During the dialogues, key considerations were noted on a flip-over (by CB). Each dialogue lasted approximately 4 h in total. Dialogues were audio-taped.

2.3 Participant selection

Selection of the participants was done via purposive sampling. In previous (interview) studies and field work (Bomhof et al., 2022; Bomhof and Bunnik, 2023), relevant groups of stakeholders had already been identified. These stakeholders were: hospital managers, health insurers, policymakers, physicians, patients, citizens and relevant professional and representatives of pharmaceutical companies, patient and physician organisations. Participants were approached by email or by telephone. Of each group of stakeholders, one representative was invited for each discussion. For the selection of the citizens, we contacted a market research bureau through which we could approach individuals who had previously attended a citizen panel regarding allocation choices in healthcare (Burgerforum, 2018). This way, we were able to ensure that our citizen-participants had basic knowledge of the Dutch healthcare system and some familiarity with questions regarding the allocation of (scarce) healthcare resources.

2.4 Dialogue format

For the design of the format for the stakeholder dialogues, we have drawn inspiration from the nominal group technique (McMillan et al., 2016) and literature on the dialogical approach (Widdershoven et al., 2009; Davies et al., 2015). Our goal was to develop a format in which stakeholders could exchange perspectives and weigh arguments together.

To help prepare for the discussion, all participants received an 'argument sheet' which we drafted in advance (see Appendix A). This argument sheet contained an overview of the moral arguments in favor of and against three policy options. One week before the dialogue, participants were asked to share their preliminary perspectives regarding the three policy options in a short online survey (see Appendix B). At the start of the dialogue, one of the research team members (EB) gave a presentation on the CL and the policy options, to make sure that each participant had sufficient background knowledge.

At the start of each dialogue, participants were asked to indicate their normative viewpoints regarding the three policy options, indicating for each policy option with a sticker on a poster (see Appendix C) whether they were "very much against" "against" "neutral" "in favor" or "very much in favor" of this policy option. Subsequently, three discussion rounds were held of approximately 1 h each. In each round, one policy option regarding access to treatments in the CL was discussed. Each discussion round was divided into three phases:

1) All participants briefly shared their perspectives regarding the policy option. Other participants could ask questions for clarification, but could not yet respond substantively to each other's arguments
2) A general discussion took place in which participants were asked to exchange views and invited to elaborate on their positions and question the perspectives of others.
3) In a final round, participants were asked to evaluate and weigh the arguments, to gauge whether or not participants had shared key considerations about the policy option.

After the three discussion rounds, participants were asked once more to indicate their normative viewpoints regarding the three policy options by putting a sticker on the poster. This way, we could determine whether stakeholders had shifted. Every dialogue was closed off with a round of reflection in which the participants gave feedback on the proceedings and shared whether they had heard any arguments that had led them to change their opinion.

2.5 Data analysis

The three audio-taped dialogues were transcribed in Word and coded using Word and NVIVO. All transcripts were independently coded using an inductive approach (by SS and CB/JS). During the coding process, weekly meetings were held with the research team to discuss the coding and straighten out discrepancies, and develop the codebook. A thematic analysis (Burgerforum, 2018) was conducted. A inductive approach was used to identify relevant themes. Both recurring overarching themes and themes per model were identified.

2.6 Ethical approval and informed consent

A waiver for this study was granted by the research ethics review committee of Erasmus MC, University Medical Centre Rotterdam (MEC-2020–0828), as the study does not fall within the scope of the WMO (the Dutch Medical Research Involving Human Subject Act).

3 Results

3.1 Sample

Of the approached stakeholders, representatives of one professional association and one pharmaceutical company did not wish to participate. Two approached patient representatives were not available at the time the dialogues were to be held, and were replaced by others. On the day of the first dialogue, a health insurer and a representative of a sector organisation had to cancel because of illness or personal circumstances. On the day of the second dialogue, the same two stakeholders had to cancel again. An overview of the participants attending the dialogues can be found in Table 1.

3.2 Themes

In this section we will first present the main findings per model and then discuss four overarching themes that surfaced during the dialogues; 1) weighing of individual interests *versus* collective

TABLE 1 Overview of the participants attending the multi-stakeholder dialogues.

Dialogue 1	Dialogue 2	Dialogue 3
1 doctor	1 doctor	1 doctor
1 citizen	1 citizen	1 citizen
1 insurer	1 insurer	1 insurer
1 patient representative	1 patient representative	1 patient representative
1 policymaker	1 policymaker	1 policymaker
1 representative of pharmaceutical companies	1 representative of pharmaceutical companies	1 representative of pharmaceutical companies
1 representative of medical professional organization	1 hospital manager	1 representative of medical professional organization
		1 hospital manager

TABLE 2 Participant quotes.

Quote	
Q1	*'. . .. I think. . .. that the Coverage Lock is meant to assess whether treatments are effective or cost-effective, and they're almost always effective, but almost never cost-effective. And then I think that we should not pay for those [treatments] from public resources if cost-effectiveness is not yet established. So then the pharmaceutical company should do it [fund these treatments].'* Participant dialogue 1
Q2	*'I think it all comes down to equality. Everything [every treatment] that someone [some physician] has to search for or negotiate for, it leads to inequality. Physicians work in different shifts and have different motivations, know different things. So I believe it leads to inequality, and that's not fair. And besides that, I think that it comes down to using public resources, as it costs time, and this time comes from public resources.'* Participant dialogue 1
Q3	*'Patients really want access, but I think I would go for the principle of equality here, which I believe is very important, that patients have equal opportunities. And again, we do not have that [equality] in the Netherlands, but we should not go and increase it [inequality] either. And if you allow patients to pay themselves, then some patients can do so and others cannot.'* Participant dialogue 1
Q4	*'People do not choose to have a low life expectancy because of their socioeconomic status. There is so much inequality already. Also regarding assertiveness and how well one knows one's way around in healthcare–I think everyone knows examples from their own social circle–I think that [inequality] is undesirable.'* Participant dialogue 2
Q5	*'It is my own money. So I should be allowed to decide whether I want to use it for my health or not. Right? It would be very strange if the government dictates that you cannot use your own money for your own health.'* Participant dialogue 3
Q6	*'Who are we to decide for someone else [that he may or may not save himself]. . .. we are talking about effective treatments (. . .), who are we then to all decide that I will swing? [that I will die]?'* Participant dialogue 3
Q7	*'It is very complicated. Actually the same as just discussed: People with money can afford it [paying for treatments]. I think, it [paying for treatments] should be allowed, but then what do we do with people who cannot afford to pay [for treatments].'* Participant dialogue 2
Q8	*'Yes, well, what you just mentioned about that neuroblastoma: if it concerns young children and it in fact looks like the treatment is effective [they should have access to that treatment].'* Participant dialogue 2
Q9	'*It is the same as [another participant] said: Every patient has the right to use all resources to save his own life. . . [Another participant answers] Well, maybe it is about the individual* versus *the collective.'* Participant dialogue 3
Q10	*'In principle I would say no [to making exceptions]: you cannot do that, if, on the one hand, you uphold a system based on solidarity, and on the other hand, you make these [exceptions] possible, that just leads to inequality, and is completely inhuman. But indeed, maybe that does not matter if it concerns young children and [the treatment] is potentially life-saving or something. But on the other hand, I think, those are exceptions and if those become the rule, then what kind of system are you left with*' Participant dialogue 2
Q11	*'In general, it seems to me that it would undermine the solidarity-based system. [Mentions a case of a young girl with neuroblastoma]. So I struggle with that, and I do not know why in that case, I do think it is appropriate [to provide access]. Maybe because there is a whole life ahead of them, that is the strongest consideration.'* Participant dialogue 2
Q12	*'It could also be used as a sort of canary in a coal mine. If we would do that [allow out-of-pocket payments], then we really have not organized the system in a right way anymore.'* Participant dialogue 3
Q13	'*I do believe that there should be a certain degree of transparency. So, from day one in which, in the Netherlands, the first patient gets treated [based on payment by a third party, including the hospital], this should be made very clear. And it should be transparent, including the conditions [for getting access to the treatment].'* Participant dialogue 1

interests, 2) shifting attitudes when confronted with other perspectives, 3) withholding access to put pressure on the system and 4) the importance of transparency regarding the CL-procedure.

In the Results section, the perspectives of participants are presented to the extent that they are relevant to describe the weighing of ethical arguments. Relevant quotes can be found in Table 2.

3.2.1 Model 1: access based on third-party payment (e.g., by pharmaceutical companies, health insurers or hospitals)

In relation to model 1, the following four themes emerged during the dialogues: 1) reasons to allow access to treatments in the CL, 2) differences between parties considered for third-party payment, 3) equality and other reasons not to provide access, 4) the role of physicians in pursuing access.

3.2.1.1 Reasons to allow access to treatments in the CL

Participants often felt that the provision of access to treatments in the CL–i.e., by third party-payment–was important, thereby relying on beneficence as an important ethical principle. Participants cited potential health benefits for patients as one of the reasons for wanting to provide access to treatments in the CL. Participants mentioned several situations in which they deemed access to treatments in the CL to be extra important: when patients are young, treatments are highly effective, or no alternative therapies are available. Some participants stated that physicians should be able to prescribe all relevant treatments, including treatments that were placed in the CL. One participant believed that all EMA-approved treatments should be available for patients as a matter of principle. However, participants also frequently mentioned concerns regarding the often-marginal benefits of newly approved treatments, and believed these should weigh in the decision whether to seek alternative access routes for treatments in the CL.

3.2.1.2 Differences between parties considered for third-party payment

During the dialogues, three potential parties for third-party payment were considered: hospitals, insurance companies and pharmaceutical companies. Most participants believed that pharmaceutical companies were a better suited third-party payer than hospitals or insurance companies, as they believed it would be unjust to use *collective* funds to pay for treatments for which (cost-) effectiveness was not yet clear (Q1). Allowing hospitals or insurance companies to pay for these treatments could undermine the role of the CL in guarding against excessive healthcare expenditures. It was felt that the CL helps to prevent expensive treatments from crowding out other forms of healthcare, as well as from usurping public spending outside the healthcare domain, for instance, in education. A second reason against allowing hospitals or insurance companies to pay, was that this use of collective funds (i.e., from hospital or insurance budgets) could weaken the government's negotiation position during price negotiations with pharmaceutical companies, because there would be less of an incentive for the latter to lower the price. Only in the third dialogue, some participants considered it appropriate if insurance agencies were to pay for treatments in the CL. Reasons given were that insurance companies would also pay for treatments once they come out of the CL, and that it would provide an opportunity for data collection on the effectiveness of these treatments in real-world settings. However, most participants were in favour of letting pharmaceutical companies pay, as pharmaceutical companies would not be using collective funds. Furthermore, some participants mentioned that letting pharmaceutical companies organize managed access programs for all eligible patients was the only way of ensuring equal access to treatments in the CL. However, it was noted that in practice, access to treatments would then solely depend on the willingness and ability of pharmaceutical companies to pay, which might result in limited or variable availability of CL treatments. To safeguard equal access, it was deemed important that payment by pharmaceutical companies would not be organized for individual patients, but–solely–through managed access programs open to all eligible patients. Furthermore, participants pointed out other (adverse) effects of allowing pharmaceutical companies to pay for treatments; firstly, pharmaceutical companies might use these programs to expand their post-CL sales opportunities. Secondly, pharmaceutical companies might account for money spent on CL-treatments during price negotiations. However, this might imply that ultimately, society ends up paying more for these treatments. Thirdly, the negotiation position of pharmaceutical companies would be undermined if they provided access for all patients while treatment are in the lock, at least in the absence of set procedures that limit the duration of the negotiation.

3.2.1.3 Equality and other reasons not to provide access

Participants also voiced concerns regarding third-party payment in general, sometimes emphasizing the importance of equal access for patients to treatments over that of individual benefits. Participants feared that third-party payment might potentially lead to arbitrariness in hospital-based decision-making about patients access to CL-treatments. They believed that patient access should not vary between hospitals or physicians, and that all eligible patients should be able to get access to relevant treatments equally. Some participants also mentioned that patient access to reimbursed forms of healthcare is currently unequal, at times, due to practice variation, and therefore wondered whether equal access to non-reimbursed treatments in this model would be a utopia. Participants also emphasized the role of the CL in safeguarding the sustainability of the healthcare system, raising concerns that all sorts of third-party payment might potentially undermine society's efforts to ensure cost-effectiveness in the allocation of healthcare resources.

3.2.1.4 The role of physicians in pursuing access

During the first two dialogues, participants also deliberated on the role physicians should play in arranging access to treatments based on third-party payment. Many participants believed that physicians should not try to arrange access as this could lead to practice variation amongst physicians and therefore enhance inequalities in patient access (Q2). For instance, some physicians might be more willing to spend time and energy pursuing treatment access or have a better network or negotiating capacities than others, giving them more opportunities to arrange access for their patients. Secondly, participants believed that arranging access to non-reimbursed treatments should not be a part of the range of duties of physicians and physicians should focus on their regular care duties. Thirdly, as arranging access costs time, participants said, it could potentially lead to physicians having less time available for other patients, thus crowding out healthcare for others (Q2). However, some participants believed that physicians should try to arrange access, mainly because of the potential health benefits for patients. One participant felt that physicians *should* pursue access if a treatment were highly effective and would lead to significant health benefits for patients. Some participants called

for transparency and clear guidelines for physicians regarding whether and when to pursue access to CL-treatments. One participant mentioned that professional associations, for example, of hematologists, should try to arrange access instead of individual physicians.

3.2.2 Model 2: Access based on out-of-pocket payments by patients

During the discussion of model 2, participants more explicitly mentioned ethical values which they believed were at stake, namely, justice, solidarity, non-maleficence and liberty.

3.2.2.1 Justice

Many participants addressed concerns regarding out-of-pocket payments increasing inequality amongst patients, as some patients would be able to pay for treatments while others would not, and therefore, allowing patients to pay was seen as unjust (Q3). Participants also mentioned that this inequality would not be 'at random' but would enhance pre-existing structural inequalities between citizens based on socio-economic status. Participants deemed equal access in healthcare to be very important. For some participants, equal access for all patients outweighed potential health benefits for individual patients. Some participants pointed out that inequality would also be enhanced in the case of crowdfunding, as some patients will have a better social network and social and financial resources to start successful crowdfunding campaigns than others. This would also exacerbate an existing divide on the basis of differences in socio-economic status (Q4). Conversely, two participants mentioned that for them, the fact that inequality already exists in the Netherlands was a reason not to consider inequality to be an important argument, especially as access to CL-treatments was seen as rare. Others responded that these existing inequalities are problematic as well, and are no justification to allow further inequalities.

Another form of injustice mentioned by participants was that, as said, out-of-pocket payments could potentially lead to the crowding out of other health services within the publicly funded healthcare system. If patients paid for treatments out of pocket, physicians would still spend time administering these treatments and patients would need follow-up care in the case of adverse events–potentially occupying hospital beds or staff, leaving less capacity for others. Some participants mentioned that patients could be allowed to pay for treatments out of pocket, but they should then also pay for any ancillary costs and additional medical care to prevent this scenario from happening.

3.2.2.2 Solidarity

Solidarity was another value frequently mentioned by participants regarding out-of-pocket payments. Participants believed that allowing out-of-pocket payments would be undermining the solidarity-based healthcare system, which would be undesirable. In addition, in the first dialogue, participants wondered whether out-of-pocket payments could lead to a shift in *perceptions* of the Dutch healthcare system: people might come to think of healthcare as purchasable and on the long-term this would lead to a decrease in experienced solidarity in healthcare in the Netherlands.

3.2.2.3 Non-maleficence

During the first dialogue, participants were concerned that not allowing out-of-pocket payments could potentially lead to patients travelling abroad to obtain these treatments. They considered this potentially harmful, as standards of care in other countries might be lower than those in the Netherlands. Nevertheless, in general, participants believed that arranging access in the Netherlands fairly, was more important than considering the harms for patients travelling abroad. However, participants also feared that *allowing* out-of-pocket payments could also be potentially harmful; namely, leading to financial harms if patients were to spend large amounts of money on expensive treatments.

3.2.2.4. Liberty

In all dialogues, participants mentioned liberty as an important value when considering out-of-pocket payments. Some participants mentioned that although they felt that equality was important, it was not deemed possible–or, by some participants, not deemed desirable–to forbid patients to pay for treatments out of pocket, placing more emphasis on the value of liberty (Q5). Participants mentioned that people should maintain their freedom to spend their money as they seem fit. Some participants believed that forbidding patients to pay for treatments, especially if these treatments could lead to significant health gains, would go 'too far'. During the third dialogue, the argument of liberty explicitly came to the fore, when a patient-representative spoke about the feeling of fear he experienced when an effective treatment for his disease was placed in the CL. This participant had wanted the freedom to arrange access to this treatment himself, if necessary (Q6). During the dialogue, other participants expressed empathy for this reasoning. However, participants were conflicted when having to weigh liberty against equality, since equal access was also deemed to be essential by many participants (Q7).

3.2.3 Model 3: No access to non-reimbursed treatments

During the third discussion round, it was notable in each of the three dialogues, that participants seemed to naturally–without extensive discussion - come to conclusions as to whether they believed access to non-reimbursed treatments should or should not be possible.

3.2.3.1 Access should be possible

A majority of the participants thought that it should be possible for physicians and patients to pursue access in one way or another (for instance through third-party payment), if physicians believed that a treatment was truly in a patient's best interest. In such cases, participants felt it was important that physicians should retain the possibility to pursue access for individual patients–to look for 'shortcuts', such as submitting individual requests to pharmaceutical companies or insurance agencies. Others believed that in such cases, access should be made possible for *all* patients–for instance through a managed access program–to ensure equal access. Participants mentioned multiple exceptional circumstances in which they believed patients should have access to treatments in the CL. Criteria which were mentioned for making such exceptions were: if patients are young, if patients are severely ill, if no alternative

therapy is available and if the treatment seems highly effective with large potential health gain for patients (Q8). Some participants also stressed that the CL is a means for guarding against insufficiently cost-effective use of collective funds, and not a goal in itself. Therefore, they believed that patients should not experience harm resulting from not being able to access treatments placed in the CL.

3.2.3.2 Access should not be possible

Some participants believed that it would be the fairest option if no-one ever had access to treatments while they were in the CL. These participants stressed that this was the most equal option, again underlining the importance of equality regarding access to healthcare. Some participants also mentioned that this option would provide the most transparency and clarity for all relevant stakeholders, including pharmaceutical companies, patients, and healthcare professionals.

3.2.4 Overarching themes

3.2.4.1 Weighing individual interests against public interests

In all dialogues, tensions between individual interests and collective interests were a recurrent theme. In all dialogues, considerations regarding individual and collective interests came hand-in-hand with debates on liberty and solidarity. On one hand, participants mentioned arguments that put the individual in the centre, for instance when the argument of freedom to spend one's own money as one sees fit was recurrently brought to the fore. The interests of the individual were also highlighted when participants elaborated on potential health gains for patients. On the other hand, participants frequently emphasized collective interests, as they stated the importance of solidarity in our healthcare system, and the collective duty to keep the healthcare system sustainable for future generations of patients. During the dialogues, participants often felt conflicted when weighing individual interests against collective interests (Q9).

3.2.4.2 Shifting attitudes

Sometimes, when, during the dialogues, participants brought up a (fictitious) concrete example of a cancer patient who would benefit from access to a treatment in the CL, other participants changed their expressed attitudes towards (dis)allowing out-of-pocket payments for treatments in the CL. Participants were inclined to "make exceptions" for these particular patients. This for instance happened when a case was brought to the fore of a young patient. One participant mentioned that inequality might matter less if the lives of young children could be saved (Q10). Some participants considered this–sometimes internal–shift puzzling and intriguing. One participant was puzzled that he considered it 'okay' to allow out-of-pocket payment for a CL treatment for a four-year-old girl with a neuroblastoma, while he had previously stated that he was against out-of-pocket payments (Q11). In another dialogue, participants noted that their weighing of the arguments would change considerably in the consulting room when face-to-face with a patient, especially when the patient-doctor relationship was a longstanding one. However, even without a longstanding relationship, it was considered very difficult for a physician *not* to help a patient arrange access to a treatment.

3.2.4.3 Withholding access to put pressure on the system

In all three dialogues, participants talked about deploying the three models strategically to put pressure on stakeholders involved in the CL-procedure to reduce the time treatments spend in the CL. For example, one participant mentioned that he was in favour of *allowing* out-of-pocket payments because this would be considered politically unacceptable in our society, and the resulting upheaval might lead to acceleration of the CL-procedure. This view was echoed in another discussion, with a participant remarking that out-of-pocket payments could be used as a kind of signal, as a 'canary in the coal mines', that the system was failing (Q12).

Pressuring the system to accelerate the CL-procedure was also mentioned as a reason to consider the model in which *no-one* would obtain access to treatments placed in the CL. Participants believed that withholding access would generate societal pressure on pharmaceutical companies and parties involved in the CL-procedure to accelerate the procedure. However, in the third deliberative discussion, one participant believed that this pressure would create much societal turmoil, which would not necessarily help move the discussion regarding the CL-procedure forward. However, others countered this statement and believed that uproar is inevitable in allocation decision-making in healthcare, pointing out that a negative reimbursement decision for a treatment would also cause uproar.

3.2.4.4 The importance of transparency regarding the CL procedure

During the dialogues, many participants stressed the importance of transparency regarding the CL-procedure. This included transparency regarding the results of price negotiations, the time which treatments spend in the lock, and possibilities for patients to access these treatments while they are in the lock. During the discussion of the first model, this last point was emphasized. Participants mentioned that it should be clear and transparent for patients and physicians how and in which hospitals patients can get access to a CL-treatment–for instance, through a managed access program–to ensure equal access to these treatments for patients (Q13). Participants also stated that it should be transparent for whom–for instance which categories of patients–access to treatments in the CL was possible, and how long the CL-procedure would take. This would help prevent societal unrest. Furthermore, participants criticized the current CL-procedure for being non-transparent about price-negotiations and treatment-prices that are eventually agreed upon. Many participants stressed the importance of a clear CL-procedure for all stakeholders–especially patients–to know where they stand. Some participants therefore were in favour of the third model, as it would provide clarity if no patients had access to treatments during the CL-procedure, while 'making exceptions' could create uncertainty.

4 Discussion

This multi-stakeholder dialogue study regarding the CL-procedure in the Netherlands showed that stakeholders have varying perspectives on access to non-reimbursed treatments. Generally, participants were in favour of allowing access–under specific circumstances–to CL-treatments so as to not withhold

potential health gains from patients in need. When discussing third-party payment, participants favoured payment by pharmaceutical companies over payment by health insurers or hospitals, as they considered it unjust to usurp collective funds while cost-effectiveness assessment was still pending. Largely, participants weighed the moral values of solidarity and equal access over the values of liberty and beneficence, and were therefore not in favour of out-of-pocket payments. The publicly funded healthcare system in the Netherlands, with an obligatory health insurance for all citizens and equal access to a basic healthcare package, is strongly based on the values of solidarity and equal access (Zorginstituut Nederland, 2022). During the dialogues, stakeholders emphasized both the importance of these values and the valuable role of policy measures such as the CL in safeguarding the sustainability of the healthcare system.

4.1 Individual *versus* collective interests

During the dialogues, four over-arching themes emerged which require ethical reflection. Firstly, it may be difficult to weigh the interests of individual patients against those of the collective in the context of access to non-reimbursed treatments. Treating physicians may need to help eligible patients gain access to treatments in the CL because of potential health benefits. This would be in line with the principle of beneficence: a physician's obligation to act to the benefit of patient (Beauchamp and Childress, 1979). In addition, one would like to allow individual patients the freedom to spend their money on medical treatments that might otherwise not be accessible, if they can and wish to do so. However, it is unclear how beneficence and liberty should be weighed against the importance of sustaining an equitable and solidary healthcare system in a country like the Netherlands.

These tensions between individual and collective interests are reflected in a recent analysis of the concept of solidarity. Solidarity may refer to various sets of norms: assisting patients in need; upholding the solidarity-based healthcare system; willingness to contribute; or promoting equality (van Till et al., 2023). In the context of (dis) allowing out-of-pocket payment for CL treatments, for instance, helping patients (crowd) fund medical treatments, can be seen as an act of solidarity on the individual or inter-individual level, but it can also be seen as undermining solidarity on a societal level, by jeopardizing the sustainability of the healthcare system or failing to promote equality. In addition, if one were a–more affluent–patient oneself, and chose to pay out of pocket for CL treatments, leaving other–less affluent–patients behind, one would be considered a failure to show solidarity towards these others patients. The results of our dialogues suggest that while stakeholders may perceive collective interests to be important, they may sometimes let individual interests outweigh collective interests, and that–at least in specific circumstances–stakeholders support patient access to treatments in the CL.

4.2 Shifting attitudes and the identifiable victim effect

Secondly, it was notable that sometimes a shift in attitudes–or expressed opinions–occurred when stakeholders discussed (fictitious) patient-cases. When confronted with detailed information about (fictitious) individual patients, participants would nuance their expressed opinions on not allowing access to treatments in the CL, and become more inclined to 'make an exception' for these particular patients. This could be explained by the so-called identifiable victim effect and the rule of rescue. According to the identifiable victim effect, people are more likely to help an identifiable victim than a statistical victim (Jenni and Loewenstein, 1997). Relatedly, according to the rule of rescue, people have a strong moral inclination to rescue the lives of *identifiable* persons in immediate danger (Jonsen, 1986). This could explain why, during the dialogues, stakeholders could discuss access models on the level of the population or healthcare system in general terms, referring to probabilities and numbers, but when concrete (fictitious) patient-cases were brought up, they changed their expressed opinions. This manifested itself clearly in the third dialogue, when a patient representative spoke about his own experiences, stating that no-one at the table truly understood what it meant to be ill and not to have access to a potentially life-saving treatment in the CL. From then onwards, participants adjusted their–at least expressed–opinions, expressing their sympathy and reasoning more in favour of access. Many participants seemed sensitive to the emotional appeal made by a patient case.

In the literature, there are ongoing debates on the merits and pitfalls of the identifiable victim effect and the rule of rescue (Daniels, 2012; Victoria, 2022). It is important to be aware of these *effects* in discussions on policy options, as they can potentially obstruct the consideration of collective interests and the equal accounting of unidentifiable victims in decision-making. As the patient perspective ought to inform decision-making, it is important that policymakers are aware of these effects, to minimize the chance of collective interests–including upholding a sustainable public healthcare system–being underrepresented in the development of policy.

4.3 Call for strategic action and transparency

The third and fourth overarching themes were closely associated. Both the call to use the models strategically to accelerate the CL-procedure and the call for more transparency regarding the CL-procedure stemmed from dissatisfaction with some aspects of the current CL-procedure. Criticism of the lack of transparency and the duration of the CL-procedure has also been found by Scheijmans et al., in their study on the experiences of stakeholders during the CL-procedure of Nusinersen (Scheijmans et al., 2022). The lack of transparency is problematic from the perspective of procedural justice. Like most priority setting agencies, the Dutch Healthcare Institute explicitly aims for just procedures for priority setting, adopting the Accountability for Reasonableness framework by Daniels and Sabin (Daniels, 2008; Zorginstituut Nederland, 2017) The first condition of the framework, the 'publicity condition', states: "decisions regarding both direct and indirect limits to care and their rationales must be publicly accessible" (29, p.45). A major obstacle in this regard is the fact that the results of price negotiations remain undisclosed, which makes it impossible for parties other than the government and

pharmaceutical companies to evaluate the reasonableness of decisions (not) to include a new treatment in the basic benefits package. Closely related is the lack of public insight into the reasons and causes of a long duration of the negotiations, for this makes it impossible to know which party (i.e., the government or the pharmaceutical company) should be held accountable for keeping patients waiting. Thus, the publicity condition, at present, remains unfulfilled.

4.4 Methodological reflection

With this study, we present a format for engagement between a diverse group of stakeholders aimed at exchanging different moral viewpoints and seeking normative common ground. Drawing inspiration from the nominal group technique (McMillan et al., 2016) and dialogical approach (Widdershoven et al., 2009; Davies et al., 2015), during the dialogues, we put emphasis on stakeholders to weigh moral arguments together. To do so, prior to the dialogues, we had sent participants an argument sheet detailing relevant moral arguments to help participants form their individual viewpoints in advance. Based on the nominal group technique, in which participants vote for various policy options, we asked participants to express a normative viewpoint regarding each policy option by placing a sticker on a Likert scale on a poster. By doing so, we were able to gain an impression whether consensus was reached, or whether shifts in individual normative viewpoints had taken place. During the dialogues, participants deliberated the different policy options and weighed the arguments pro and con. However, it proved difficult to ask stakeholders to develop *common* normative ground. During the dialogues, we have asked whether–and on which views–participants agreed, but we did not continue to steer towards reaching a consensus if stakeholders had opposing views. This study can be characterized as a normative policy orientated bioethics (NPOB) project (Ives and Draper, 2009), as it tried to integrate empirical findings from our previous research with normative recommendations of stakeholders by using a dialogical approach. As mentioned above, the aim of this study was to see whether multi-stakeholder dialogues could be used to exchange viewpoints and seek for common normative ground. In our study it proved difficult to arrive at definite normative conclusions or consensus. However, whether consensus should be the ultimate goal of such dialogues is questionable, as in a pluralistic democracy, reasonable pluralism–a plurality of reasonable, though irreconcilable moral views–seems a given (Rawls, 1993). So while during the dialogues there was no consensus on the moral dilemma of whether to allow access to non-reimbursed treatments, which was neither expected nor perhaps necessary, stakeholders did arrive at some common normative ground regarding procedural aspects and recognition of certain values. For instance, the importance of taking into account both collective and individual interests, and of the transparency of access routes to non-reimbursed treatments. In the field of empirical bioethics, there is some debate on whether dialogue can be used to derive normative conclusions. Some believe that consensus can have some moral authority, for instance in the context of clinical decision-making (Walker and Lovat, 2022). While we believe that consensus alone does not constitute sound ethical conclusions, this study shows that a dialogical approach can be useful to deepen moral viewpoints and gain a better understanding of moral dilemmas based on the perspectives of stakeholders (Widdershoven et al., 2009). Furthermore, it can help stakeholders in enriching their moral perspectives and understanding the perspectives of others which might help them in decision-making. With this, we might reach the limits of what normative ethics can achieve in a situation of reasonable pluralism and opposing moral views. For future research, it would be interesting to investigate the role of political philosophy, such as deliberative democracy (Rawls, 1993), to integrate the empirical and normative and support political decision making in the face of deep seated reasonable moral pluralism. Furthermore, it would be interesting to asses in which extent the outcomes of such dialogues influence stakeholders' decision-making in practice.

4.5 Strengths and limitations

This study had several strengths and limitations. For this study, we were able to bring together many different stakeholders, including hospital managers, health insurers, policymakers, physicians, patients, citizens, and representatives of pharmaceutical companies, relevant professional, and patient organizations in the field. This resulted in the presence of a broad range of views, helping participants to discover different perspectives and learn from other stakeholders. Furthermore, the dialogues were held in a safe and confidential environment, which had a positive influence on the exchange of views. In total, three dialogues were conducted, to prevent the potential occurrence of groupthink to influence the results. We observed that there were no substantial differences in themes across the three dialogues. We explicitly wanted to involve–informed–citizens in the dialogues, and have tried to provide an equal minimum of background knowledge by providing information beforehand and starting each dialogue with a presentation. However, during two of the three dialogues, citizens were sometimes less involved in the discussion as other stakeholders, as differences in background knowledge were still present. The duration of the dialogues (4 hours) gave room for an extensive exchange of views, and at the end of the dialogues, no new themes emerged. However, some participants mentioned they would have preferred to discuss the topic further–including alternative policy options.

5 Conclusion

These multi-stakeholder dialogues emphasize the importance of stakeholder engagement in policy development regarding the sustainability of the healthcare system. Dialogues between stakeholders with varying perspectives on access to treatments in the CL have proved useful to help validate and deepen the moral arguments for and against three models for access to treatments in the CL. Generally, most stakeholders were in favour of allowing access–at least when treatments are clearly beneficial–to treatments in the CL. When discussing third-party payment, stakeholders favoured payment by pharmaceutical companies over payment by

health insurers or hospitals, not wanting to usurp collective funds while cost-effectiveness assessments are still pending. Largely, stakeholders were not in favour of out-of-pocket payments, emphasizing solidarity and equal access as important pillars of the Dutch healthcare system. In order to safeguard equal access as much as possible, various stakeholders stressed the importance of transparency as to in which hospitals CL treatments are available by means of managed access. In addition, the call was made for clear and consistent procedures to ensure such transparency, and to reduce the administrative workload for physicians, also in order to prevent displacement of care resulting from excessive burdens on physicians. Policies for access to non-reimbursed treatments should address stakeholders' concerns regarding transparency, equal access and solidarity, and potential loss of health benefits for patients. Multi-stakeholder dialogues are an important tool to help inform policy-making on access to newly approved, expensive treatments, in the Netherlands, and in other countries dealing with the growing challenges that these treatments pose to the sustainability of the healthcare system.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

CB: Conceptualization, Formal Analysis, Investigation, Methodology, Writing–original draft. JS: Conceptualization, Formal Analysis, Investigation, Methodology, Writing–review and editing. SS: Formal Analysis, Writing–original draft. MS: Conceptualization, Funding acquisition, Investigation, Methodology, Writing–review and editing. EB: Conceptualization, Funding acquisition, Investigation, Methodology, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study is a result of the research project 'Ethical access and reimbursement models for expensive new cancer treatments: How to reconcile diverging values?', which was funded by the Dutch Cancer Society, project number 12473 (2020-2023).

Acknowledgments

The authors would like to thank all participants of the dialogues for their valuable input.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1265029/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 14 February 2024
DOI 10.3389/fphar.2024.1338541

OPEN ACCESS

EDITED BY
Denise Van Den Berg,
Treatmeds Foundation, Netherlands

REVIEWED BY
Anke Pisters-van Roy,
CZ Health Insurance, Netherlands
Aniek Dane,
Erasmus Medical Center, Netherlands

*CORRESPONDENCE
Gro Live Fagereng,
gfageren@ous-hf.no

RECEIVED 14 November 2023
ACCEPTED 25 January 2024
PUBLISHED 14 February 2024

CITATION
Fagereng GL, Morvik AM, Reinvik Ulimoen S, Ringerud AM, Dahlen Syversen I and Sagdahl E (2024), The impact of level of documentation on the accessibility and affordability of new drugs in Norway.
Front. Pharmacol. 15:1338541.
doi: 10.3389/fphar.2024.1338541

The impact of level of documentation on the accessibility and affordability of new drugs in Norway

Gro Live Fagereng[1,2]*, Anne Marit Morvik[3], Sara Reinvik Ulimoen[1,4,5], Anne Marthe Ringerud[1], Iselin Dahlen Syversen[1] and Erik Sagdahl[1,6]

[1]The Pharmaceutical Division, The Norwegian Hospital Procurement Trust, Vadsø, Norway, [2]Institute for Cancer Research, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway, [3]Norwegian Medical Products Agency, Oslo, Norway, [4]South-Eastern Norway Regional Health Authority, Hamar, Norway, [5]Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust, Drammen, Norway, [6]Department of Pharmacy, The Arctic University of Norway, Tromsø, Norway

Introduction: Over the preceding decade, an increasing number of drugs have been approved by the European Medicines Agency (EMA) with limited knowledge of their relative efficacy. This is due to the utilization of non-randomized, single-arm studies, surrogate endpoints, and shorter follow-up time. The impact of this trend on the accessibility and affordability of newly approved drugs in Europe remains uncertain. The primary objective of this study is to provide insights into the issues of accessibility and affordability of new drugs in the Norwegian healthcare system.

Method: The presented study entails an analysis of all reimbursement decisions for hospital drugs in Norway spanning 2021–2022. The included drugs were approved by the EMA between 2014 and 2022, with the majority (91%) receiving approval between 2018 and 2022. The drugs were categorized based on the level of documentation of relative efficacy. Approval rates and costs (confidential net-prices) were compared.

Results: A total of 35% (70/199) of the reimbursement decisions were characterized by limited certainty regarding relative efficacy and as a consequence the Norwegian Health Technology Assessment (HTA) body did not present an incremental cost-effectiveness ratio (ICER) in the HTA report. Within this category, a lower percentage of drugs (47%) gained reimbursement approval compared to those with a higher certainty level, which were presented with an ICER (58%). On average, drugs with an established relative efficacy were accepted with a 4.4-fold higher cost (confidential net-prices). These trends persisted when specifically examining oncology drugs.

Conclusion: Our study underscores that a substantial number of recently introduced drugs receive reimbursement regardless of the level of certainty concerning relative efficacy. However, the results suggest that payers prioritize documented over potential efficacy. Given that updated information on relative efficacy may emerge post-market access, a potential solution to address challenges related to accessibility and affordability in Europe could

involve an increased adoption of market entry agreements. These agreements could allow for price adjustments after the presentation of new knowledge regarding relative efficacy, potentially resolving some of the current challenges.

KEYWORDS

drugs, net-prices, reimbursement, managed-entry agreement, oncology, medicinal product, European Medicines Agency, Health Technology Assessment

1 Introduction

The rising cost of medicines is a significant burden on healthcare systems. Globally, there was a 13% increase in annual expenditure on medicines from 2019 to 2022, independent of COVID-19 (Tichy et al., 2022; Pritchett et al., 2023). This upward trend is primarily attributed to the growth in the cost of new drugs, while increased utilization and prescriptions have had a relatively low impact (Parasrampuria and Murphy, 2022; Pritchett et al., 2023). In the United States, there has been a 20% increase in launch prices for new drugs over the last decade (Rome et al., 2022). To control the growing expenses for pharmaceuticals, European countries are implementing new procurement practices such as reference pricing, public tendering, price discounts, prescription guidelines for physicians, and generic substitution (European Commission, 2022).

The World Health Organization (WHO) recommends implementing health technology assessments (HTAs) to inform reimbursement decisions, a practice adhered to by 40% of all member countries (WHO, 2023). In Norway, the decision on public reimbursement is based on various aspects, including a cost-utility analysis provided by the market authorization (MA) holder and evaluated by the Norwegian Medicinal Products Agency (NOMA). The analysis compares the new drug with the existing treatment alternative and calculates the incremental cost-effectiveness ratio (ICER). The ICER considers both the cost and utility of both the new and the old drug (NICE, 2008). The established relative efficacy, meaning the comparison (direct or indirect) of treatment outcomes between a new drug and standard-of-care for a given indication, provides a more robust estimate of the ICER compared with potential efficacy, meaning single-arm studies, non-adjusted indirect comparisons based on, e.g., response rate or duration of response only.

There has been an increased number of submissions to the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) based on limited knowledge of relative effect, long-term effect, and side effects due to the use of non-randomized, single-arm studies, surrogate endpoints, and shorter follow-up time (Goring et al., 2019; Del Paggio JC et al., 2021). This trend is partially due to the introduction of expedited approval programs for drugs in situations where comprehensive data cannot be provided and where the benefit of immediate availability outweighs the risk. Limited knowledge of relative efficacy is challenging HTA evaluation and reimbursement decisions (Vreman et al., 2020). To a certain extent, HTA methodologies have adapted; for example, there is an increased use of external control arms. However, this has consequently led to a reduction in the robustness of the HTA evaluation (Burger et al., 2021; Jaksa et al., 2022).

In Norway, HTAs are systematically used at the national level, primarily employing cost-utility analyses as a tool for making informed decisions on whether to introduce new interventions into healthcare services (reimbursement decision). In Norway, the decision-making process for reimbursement considers three prioritization criteria: benefit, resources, and severity. These factors are all incorporated into the reimbursement decision process. A cost-utility analysis provides an assessment of benefit (gain in quality-adjusted life years, QALYs) and resources/incremental costs. Further, the severity of the disease in question is operationalized as an absolute shortfall, measured in QALY loss. However, in cases where the HTA body (NOMA) considers the clinical documentation to be inadequate to establish a robust estimate of relative efficacy, the cost-utility model is not assessed, and hence, no ICER is presented to the payers. In cases where the cost-utility model is not assessed, the priority criteria cannot be evaluated by these tools; hence, a more limited assessment of incremental effect (if applicable) and annual treatment costs (based on confidential net prices) is undertaken. Hence, based on an overview of drugs for which it was possible to present an ICER or not, drugs can be categorized by the robustness of evidence of therapeutic benefit.

This paper summarizes the reimbursement decisions for all new hospital-financed drugs introduced to the Norwegian market between 2021 and 2022. The primary objective is to provide insights into the impact of the level of documentation on the accessibility and affordability of new drugs in the Norwegian healthcare system and to compare accessibility to countries with a similar system for reimbursement. Additional analyses were directed specifically toward oncology drugs, as a substantial proportion of drugs approved by EMA through expedited approval programs, such as conditional approvals are in this therapeutic area (Hwang et al., 2022).

2 Methods

All reimbursement decisions, along with corresponding NOMA appraisals, for hospital financed drugs between 1 January 2021, and 31 December 2022, were accessed through www.nyemetoder.no. Decisions that solely considered price per gram, non-drug decisions (e.g., diagnostics), and decisions made without price information were excluded. Only decisions relevant for cost-utility analysis were included (see Supplementary Table S1).

The NOMA appraisals were reviewed to determine whether comparative clinical efficacy was evaluated by NOMA. The drugs were classified into three categories:

1) Drugs with a clinically comparable drug already reimbursed for the given indication (a cost-utility analysis is not considered necessary as the treatment cost of the already

TABLE 1 All decisions on reimbursement of hospital financed drugs in Norway in the period 2021–2022. Decisions considering only price per gram, non-drug decisions (e.g., diagnostics), and decisions made without price information were excluded. All decisions relevant for cost-utility analysis were included. CUA: Cost-utility-analysis.

238	Decisions on reimbursement by the regional health authorities in Norway 2021–2022
3	Price per gram
22	Non-drug decisions
14	Decisions without price information
199	Decisions on drugs were CUA were relevant
90	Decisions on oncology drugs were CUA were relevant

reimbursed drug serves as an anchor in a cost-minimization analysis).

2) Drugs presented with an ICER based on a cost-utility model evaluated by NOMA (relative efficacy presented to payers).
3) Drugs presented without an ICER or cost-utility models evaluated by NOMA and without any reimbursed comparable drugs (relative efficacy not presented and no cost-anchor present).

To analyze oncology drugs separately all reimbursement decisions for oncology indications, as defined by NOMA, were reviewed separately.

To analyze the reimbursement decisions and market entry of each category, we compared the proportion of positive approvals and annual treatment costs (standard dosing) per patient using both launch prices and the confidential rebate prices. Information was extracted from publicly available databases on reimbursement decisions (nyemetoder.no) and published HTA reports by NOMA. Confidential rebate prices were accessed through The Norwegian Hospital Procurement Trust. All information about each reimbursement decision was combined and stored at the Norwegian Hospital Procurement Trust. All authors have access to the complete dataset.

Information about the status of reimbursement decisions in England, Sweden, and Denmark at the time of the reimbursement decision in Norway is provided by the Norwegian Hospital Procurement Trust as part of the price information to the payers. The data is publicly available at nyemetoder. no.

Statistical analysis: The differences in cost are based on the average cost in each drug category, while the graphical description is based on z-score normalization.

3 Results

Between 2021 and 2022, a total of 238 reimbursement decisions were made for hospital-financed medicinal products in Norway, involving 176 unique medicinal products/indications, as some products had several decisions. Among these decisions, 199 were relevant for cost-efficacy analysis according to the Norwegian reimbursement system (Table 1). Decisions considering only price per gram, non-drug decisions (e.g., diagnostics), and decisions made without price information were excluded. All decisions relevant for cost-utility analysis were included. The drugs were separated into three categories based on the level of documentation regarding therapeutic benefit. Out of the 199 decisions, 41% (81/199) had a clinically comparable drug already reimbursed in Norway, 24% (48/199) had certainty regarding relative efficacy (presented with an ICER), and 35% (70/199) had uncertainty regarding relative efficacy (presented without an ICER) (Figure 1A).

Of the 199 decisions in Norway during the period 2021–2022, 45% (90/199) were decisions on oncology drugs. Among these decisions, 28% (25/90) had a comparable drug already reimbursed in Norway, 33% (30/90) had documentation on relative efficacy (presented with an ICER), and 39% (35/90) had limited documentation on relative efficacy (presented without an ICER) (Figure 1B).

3.1 Proportion of positive reimbursement decision depending on the robustness regarding evidence of relative efficacy

The proportion of positive reimbursement decisions for each of the three categories was examined. Among drugs entering the market where a clinically comparable drug was already reimbursed, 69% were approved for reimbursement. For drugs with documentation on relative efficacy (presented with an ICER), 58% were approved for reimbursement, while for drugs with limited documentation (no ICER presented), 47% were approved (Figure 1C). Similar proportions of reimbursement approvals were observed for oncology drugs (Figure 1D).

The reimbursement system in Norway shares similarities with those in Sweden, Denmark, and England. The national launch dates of new drugs are, on average, comparable between the countries (Büssgen and Stargardt, 2022). The documentation requested from the national HTA agencies is similar. However, unlike NOMA, the HTA bodies in Sweden, Denmark, and England evaluate the cost-utility model irrespective of the level of documentation (personal communication, June 2023). To examine the possible impact of the different approach in HTA assessment on access, we compared reimbursement status in Sweden, Denmark, and England at the time of the decision in Norway for all drugs considered by NOMA to have uncertain relative efficacy (Figure 2). England had already approved 44% of these drugs, while Sweden and Denmark had approved 25% and 22%, respectively, compared to a 47% approval rate in Norway. The majority of the drugs not approved in the respective countries were either still under evaluation or not considered for evaluation.

3.2 Comparison of annual treatment cost (based on confidential net prices)

By comparing the annual treatment costs for the three categories of drugs (Figure 3), we can explore the variation in confidential net prices for reimbursed drugs. Hospital-financed drugs supported by documentation regarding relative efficacy are, on average, accepted for reimbursement with a cost that is 4.4 times higher (confidential net price) than drugs with limited documentation (Figure 3A). Hospital drugs entering the market without clinically comparable

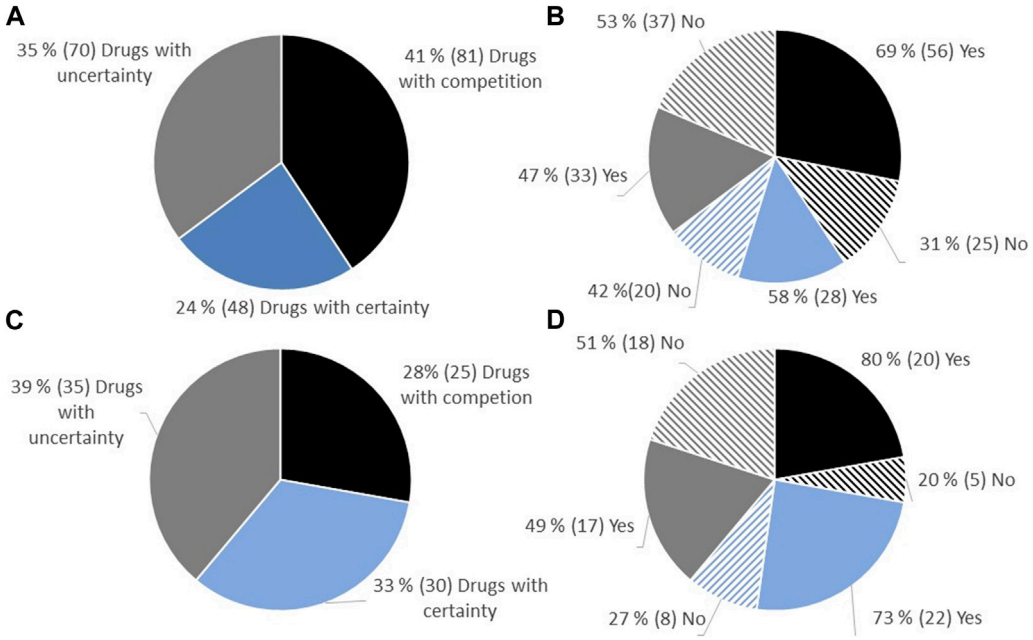

FIGURE 1
(A) Overview of the proportion of approval regarding reimbursement of new hospital-financed drugs in Norway in the period 2021–2022, split into categories depending on the level of uncertainty. **(B)** Proportion of approval in the different categories. **(C)** All decisions on reimbursement of oncology drugs. **(D)** Proportions of approval of oncology drugs depending on category.

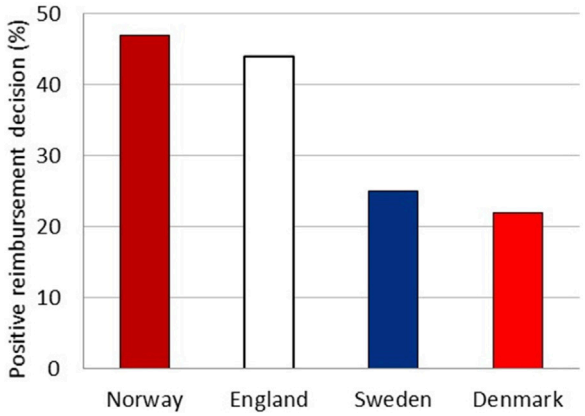

FIGURE 2
Total percentage of drugs with a positive reimbursement decision in England, Sweden, and Denmark at the time of the decision in Norway.

drugs already reimbursed and with documentation on relative efficacy are on average accepted with a 4.0 times higher cost (confidential net prices) compared to drugs entering a market where there is already a comparable drug reimbursed.

Focusing specifically on oncology drugs, those with documentation on relative efficacy are on average accepted for reimbursement with a 3.3 times higher cost level (confidential net prices) compared to oncology drugs without such documentation. Oncology drugs entering the market when there is no clinically relevant treatment alternative available are accepted with treatment costs that are on average 1.4 times higher than drugs entering a market with a clinically relevant competing drug already reimbursed (Figure 3B).

3.3 Correlation between launch price and confidential net price

To investigate whether the difference in the certainty of estimated relative efficacy is reflected in the pricing strategies of pharmaceutical companies, an analysis of the cost difference was conducted based on the list-price of all drugs and reimbursed drugs separately (Figure 4). The comparisons of list prices for the three categories were performed by considering annual treatment costs per patient. There was a high variation in list prices in all categories, and no trend towards differences in list prices of drugs based on the level of documentation was observed (Figure 4A). However, drugs with a comparable drug already on the market had a significantly lower list price (2.2 times lower on average) compared to drugs without such competition. When considering only reimbursed drugs (Figure 4B), the difference reemerged. Drugs with robust documentation on relative efficacy (presented with an ICER) were on average 3 times more expensive than drugs with less robust documentation (without an ICER) and 2.8 times more expensive than drugs with clinically comparable competition.

When examining oncology drugs separately, both drugs with uncertainty and drugs with competition had an average lower list price (1.7 and 1.3, respectively) compared with drugs with certainty regarding relative efficacy (Figures 4C, D). The same pattern can be seen for reimbursed oncology drugs, with drugs with certainty regarding relative efficacy having an average list price 1.7 and 1.3 times higher than drugs with uncertainty regarding relative efficacy or competition already on the market, respectively.

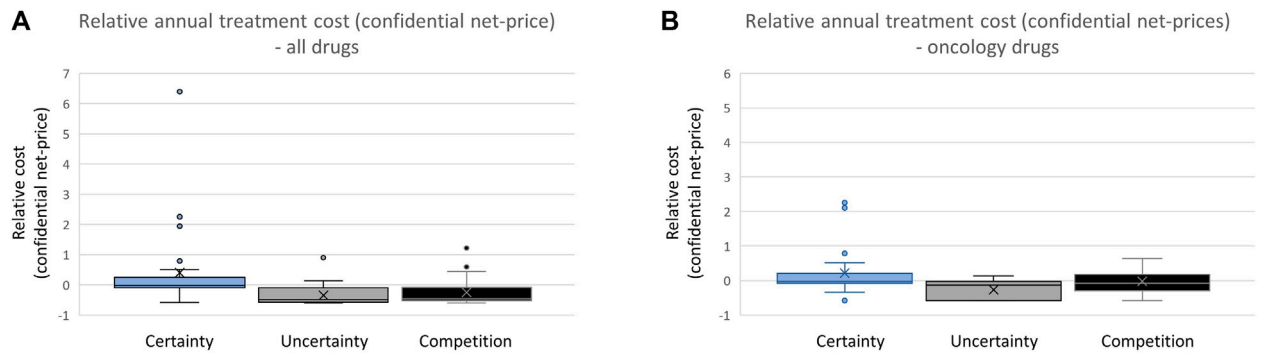

FIGURE 3
(A) Comparing annual treatment cost of all reimbursed drugs in the period 2021–2022. **(B)** Comparing annual treatment cost of all reimbursed oncology drugs.

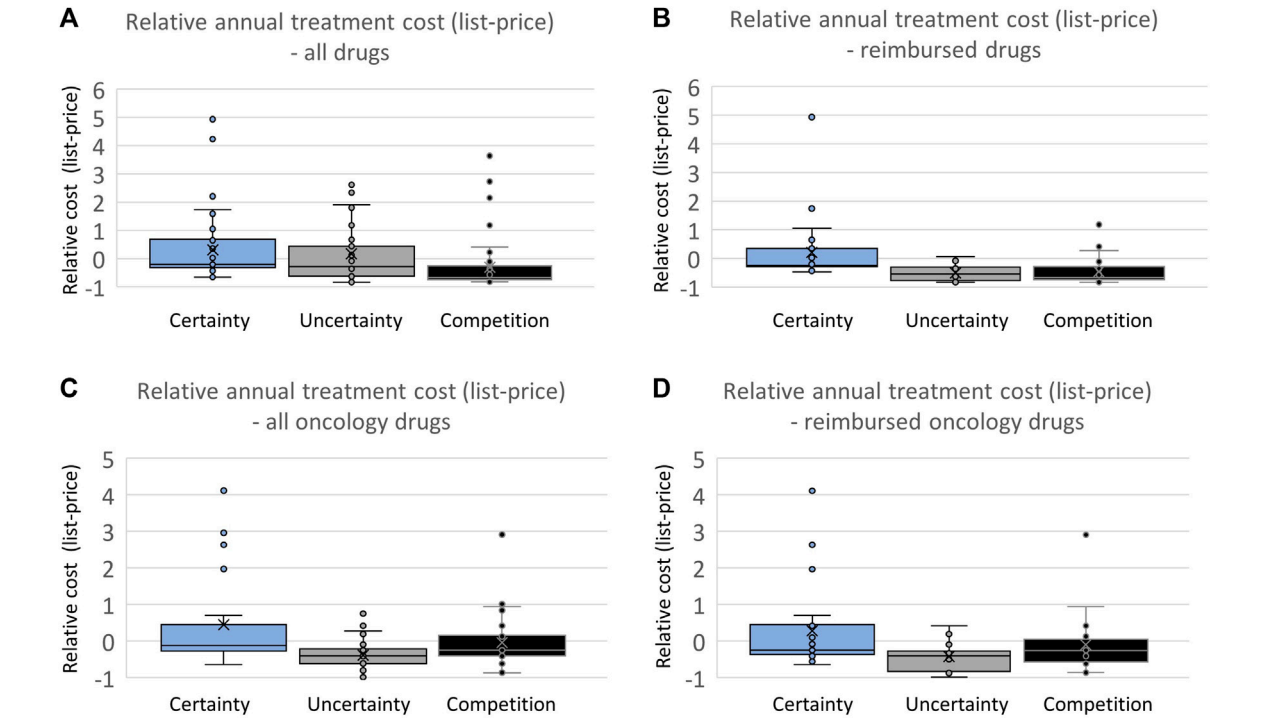

FIGURE 4
(A) Comparing annual treatment cost based on the list price of all drugs. **(B)** Comparing annual treatment cost based on the list price of all reimbursed drugs. **(C)** Comparing annual treatment cost based on the list price of all oncology drugs. **(D)** Comparing annual treatment cost based on the list price of all reimbursed oncology drugs.

4 Discussion

The Norwegian reimbursement system is based on cost-utility analyses, providing an assessment of utility (gain in quality-adjusted life years, QALYs) and resources/incremental costs. In cases where the HTA agency (NOMA) deems the clinical documentation inadequate for establishing a robust estimate of relative efficacy, the cost-utility model remains unassessed, leading to the absence of an ICER. The results presented here indicate that a significant number (35 %) of reimbursement decisions are based on limited documentation regarding the relative efficacy drugs. A similar pattern is observed when analyzing oncology drugs separately. This aligns with the development in clinical trial methodologies, characterized by the utilization of surrogate endpoints, shorter follow-up periods, and single-arm trials, all of which have introduced increased uncertainties in the HTA process (Goring et al., 2019; Grimm et al., 2019; Del Paggio et al., 2021; Trapani et al., 2022; Merino et al., 2023).

Uncertainty about efficacy may result in delays in the pricing and reimbursement process, as therapeutic value and the quality

of evidence are decisive factors for reimbursement (Malinowski et al., 2018; Galeone et al., 2021; Jommi et al., 2021; Siegmeier and Büssgen, 2022; EFPIA, 2023). This is also seen in Norway, where a lower proportion of reimbursement approvals is observed for drugs with limited documentation available. Similar patterns emerge when examining oncology drugs separately. These findings underscores that the level of documentation of relative efficacy and the presence of comparable drugs already reimbursed influence the probability of reimbursement in Norway.

Approximately half of all drugs approved by the EMA demonstrate meaningful clinical benefit according to the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (ESMO-MCBS) grades (Booth and Del Paggio, 2017; Vivot et al., 2017; Tibau et al., 2018). However, several studies show no consistent relation between assumed clinical benefit and cost (Vivot et al., 2017; Mailankody and Prasad, 2015; Salas-Vega et al., 2020; Saluja et al., 2018; Vokinger et al., 2020). In Italy, examining confidential net prices revealed a correlation between the annual cost of drugs and therapeutic benefit (Jommi et al., 2021). This finding is consistent with our results from Norway, where a lack of evidence of added therapeutic benefit correlates with lower drug costs (confidential net prices). These results emphasize the importance of documented clinical benefit when considering reimbursement of new drugs, and documentation of relative efficacy justifies higher cost levels when drugs enter the Norwegian market.

When considering list prices for all drugs, no differences were observed between drugs. However, when looking only at drugs accepted for reimbursement, the cost difference reemerged, indicating that some companies have a pricing strategy reflecting the current level of documentation regarding relative efficacy. In Europe, there is an increasing utilization of managed entry agreements to address challenges associated with escalating drug costs and heightened uncertainty regarding clinical benefits (Ciulla et al., 2023). Interestingly, competition from on-patent clinically comparable drugs reduced both the list price and the confidential net price of new drugs. This effect was observed even when considering only oncology drugs. In terms of confidential net price, this outcome may reflect the utilization of tendering processes for on-patent clinically comparable drugs in Norway. If a new drug within a treatment group wins the tender, it can acquire a significant market share, leading to 70%–100% of all new patients starting treatment with the new drug.

All oncology drugs receiving accelerated approval by the FDA before November 2018 have been converted to traditional approval through supplementary confirmatory studies (Beaver et al., 2018; Subbiah et al., 2022). EMA's human medicines committee (CHMP) recently recommended not renewing the conditional marketing authorisation for Blenrep (belantamab mafodotin), a medicine used to treat multiple myeloma. At the time of the initial authorisation, no comparative data for Blenrep were available. The recent recommendation follows a review of available data by the CHMP as part of the renewal of Blenrep's marketing authorisation. In its review, the CHMP considered that results from a new study did not confirm the effectiveness of Blenrep as agreed when conditional marketing authorisation was granted (EMA, 2023). A reevaluation of cost-efficacy analyses reveals a high degree of variation between pre- and post-market entry (Guggenbickler et al., 2022), highlighting the disparity between the estimated patient benefit at the time of market entry and the perceived patient benefit in clinical practice. This aligns with observational studies examining survival data, indicating improvement in survival for certain cancer indications, while demonstrating limited or no effect in others (Neyt et al., 2023). In conclusion, early market entry heightens the risk of introducing inefficient drugs, into the clinical setting without a comprehensive follow-up plan aimed at closing knowledge gaps and with option to reassess reimbursement decisions. Monitoring post-marketing efficacy should be conducted with the same level of rigor as post-marketing safety. Extensive long-term analyses have revealed that approximately 70 % of FDA approved orphan drugs undergo safety-related labeling changes, although severe safety events are rare (Fan et al., 2022). The implementation of post-marketing surveillance serves the dual purpose of ensuring early access to treatments while concurrently prioritizing patient safety.

The discrepancy between perceived and documented value can be addressed through the implementation of managed entry agreements, as evidenced by the increasing adoption of such agreements (Jommi et al., 2020; Efthymiadou and Kanavos, 2022). The complexity associated with managed entry agreement implementation remains a challenge and contributes to extended time frames for the final reimbursement decision (Kang et al., 2020; Eichler et al., 2021; Fens et al., 2021). To optimize the utilization of managed entry agreements, it is essential to incorporate them into the pricing strategies of pharmaceutical companies. A mutually agreed-upon strategy for assessing the clinical benefit of new drugs is crucial for ensuring patient access (Pignatti et al., 2022; Xoxi et al., 2022). Both the pharmaceutical industry and regulatory entities recognize that, in some situations where a randomized study is not feasible, real-world data can offer a valuable comparison to quantify relative efficacy. Nonetheless, moving forward, the development of clear guidelines will be necessary to guide the use of real-world data in such contexts (Burger et al., 2021).

Reimbursement agencies are mainly concerned with proven health gain when procuring new drugs. However, incentives for innovation are important for the development of new drugs, as emphasized by the EU pharmaceutical strategy (European Commission, 2020). This is supported by providing the possibility of early market entry, but for this to be successful, it must also lead to reimbursement. To achieve this aim, the pricing and market strategy should reflect the level of documentation at market entry. However, often more information regarding relative efficacy comes after market entry. One strategy can be the use of managed entry

agreements that allow for a reduced price level at the time of reimbursement and potential price increase over time if new documentation on relative efficacy is provided.

Data availability statement

The datasets presented in this article are not readily available because the confidential net-prices cannot be shared. Requests to access the datasets should be directed to www.sykehusinnkjop.no.

Author contributions

GF: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing–original draft, Writing–review and editing. AM: Data curation, Writing–review and editing. SR: Conceptualization, Writing–review and editing. AR: Supervision, Writing–review and editing. IS: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing–review and editing. ES: Conceptualization, Project administration, Resources, Supervision, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Norwegian Hospital Procurement Trust.

Acknowledgments

The authors would like to acknowledge the staff of the Norwegian Hospital Procurement Trust, the South-Eastern Norway Regional Health Authority, and the Norwegian Medical Products Agency for all their feedback.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1338541/full#supplementary-material

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TYPE Review
PUBLISHED 28 March 2024
DOI 10.3389/fphar.2024.1369805

OPEN ACCESS

EDITED BY
Sahar Barjesteh Van Waalwijk Van Doorn-Khosrovani,
CZ Health Insurance, Netherlands

REVIEWED BY
Netsanet Gebeyehu,
St. Peter's Specialized Hospital, Ethiopia
Fenglei Huang,
Boehringer Ingelheim, Germany

*CORRESPONDENCE
C. A. M. van Riel,
charlotte.vanriel@radboudumc.nl

RECEIVED 13 January 2024
ACCEPTED 04 March 2024
PUBLISHED 28 March 2024

CITATION
van Riel CAM, Michielsens CAJ, van Muijen ME, van der Schoot LS, van den Reek JMPA and de Jong EMGJ (2024), Dose reduction of biologics in patients with plaque psoriasis: a review.
Front. Pharmacol. 15:1369805.
doi: 10.3389/fphar.2024.1369805

Dose reduction of biologics in patients with plaque psoriasis: a review

C. A. M. van Riel[1,2]*, C. A. J. Michielsens[1,2], M. E. van Muijen[3,4], L. S. van der Schoot[1,2], J. M. P. A. van den Reek[1,2] and E. M. G. J. de Jong[1,2,5]

[1]Radboud University Medical Centre, Nijmegen, Netherlands, [2]Department of Dermatology, Radboud University Medical Centre, Nijmegen, Gelderland, Netherlands, [3]Maastricht University Medical Centre, Maastricht, Limburg, Netherlands, [4]Department of Dermatology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands, Netherlands, [5]Radboud University, Nijmegen, Gelderland, Netherlands

Dose reduction (DR) of first-generation biologics for plaque psoriasis (TNF-alpha inhibitors (i) and interleukin (IL)-12/23i) has been described in a previous scoping review. The literature on the DR of the newest generation of biologics (IL-17/23i) was scarce. The current review provides a literature update on the previous scoping review on the DR of all biologics, including the newest generation, with a focus on the uptake and implementation of DR in practice. The current literature search on DR revealed 14 new articles in addition to those in the previous review. Four of the newly found articles tested DR strategies, mostly focusing on first-generation biologics; only guselkumab (IL-23i) was included in one study. The other 10 studies showed data on regaining response after failure of DR, safety, cost-effectiveness, and uptake and implementation, as well as information about IL-17/23i. The eligibility criteria to start DR included both absolute and relative Psoriasis Area and Severity Index (PASI) scores (PASI ≤3/≤5/PASI 75–100) and/or Dermatology Life Quality Index (DLQI) ≤3/≤5, or BSA ≤1/≤2, or Physician Global Assessment (PGA) ≤1/0–2 during a period ranging from 12 weeks to ≥1 year. Most studies used PASI ≤5 and/or DLQI ≤5 or PGA ≤1 for ≥6 months. DR strategies were mostly performed by stepwise interval prolongation in two steps (to 67% of the standard dose, followed by 50%). Some studies of IL-17/23i reduced the dose to ±25%. The tested DR strategies on stepwise or fixed DR on TNF-αi and IL-12/23i (three studies), as well as one "on-demand" dosing study on IL-23i guselkumab, were successful. In the case of relapse of DR on TNF-αi and IL-12/23i, clinical effectiveness was regained by retreatment with the standard dose. All studies showed substantial cost savings with the biologic DR of TNF-αi and IL-12/23i. The identified barriers against the implementation of DR were mainly a lack of guidelines and scientific evidence on effectiveness and safety, and a lack of time and (technical) support. The identified facilitators were mainly clear guidelines, feasible protocols, adequate education of patients and physicians, and cost reduction. In conclusion, DR seems promising, but a research gap still exists in randomized, prospective studies testing DR strategies, especially of IL-

17/23i, hampering the completion of guidelines on DR. Taking into account the identified barriers and facilitators most likely results in a more successful implementation of biologic DR in practice.

KEYWORDS

psoriasis, dose reduction, dose tapering, clinical practice, implementation, biologics, biologicals, (cost-)effectiveness

1 Introduction

Psoriasis is a chronic immune-mediated skin disease causing a global burden, both clinically and economically, and affects approximately 2%–3% of the world population (Ghoreschi et al., 2021). Treatment options for psoriasis have increased in the past decades with the introduction of biologics. The first generation of biologics consisted of the tumor necrosis factor-alpha (TNF-α) inhibitors (infliximab, adalimumab, etanercept, and certolizumab pegol) and the interleukin (IL-)12/-23 inhibitor (ustekinumab). The newest generation of biologics entered the market more recently and includes IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab) and IL-23 inhibitors (guselkumab, risankizumab, and tildrakizumab). Biologics have been proven to be effective in patients with moderate-to-severe plaque psoriasis (Armstrong et al., 2020). However, they are also expensive and carry a risk of adverse events like infections and injection site reactions (Scherer et al., 2010; Gisondi et al., 2015; Reich et al., 2015; Snast et al., 2017; Thomaidou and Ramot, 2019; Armstrong et al., 2020). In general, biologics are prescribed in standard dosages, although previous research showed that patients with good treatment responses might be overtreated with these standard dosages (Menting et al., 2015). Therefore, exploring possibilities for the dose reduction (DR) of biologics in patients with plaque psoriasis is important. DR by prolongation of the injection interval of adalimumab, etanercept, and ustekinumab has proven to be effective, safe, and cost-effective in patients with stable low disease activity (Atalay et al., 2020a). A previous scoping review by Michielsens et al. (2021) provided a broad overview of the available literature on DR in adult patients with plaque psoriasis up to April 2020. This review showed that the available literature regarding the DR of the newest generation of biologics was scarce. The availability of sufficient literature on DR of both the first- and newest generation of biologics, as well as on the implementation of DR strategies, is important for incorporating DR in clinical practice. Therefore, the aim of this review is to provide an update on the previous scoping review on biologic DR by Michielsens et al. (2021) of all biologics, including the newest generation biologics, with as new aspect the uptake and implementation of DR in clinical practice.

2 Methods

PubMed was searched for literature between 1 January 2020 and 5 July 2023. We chose 2020 as the search of the previous review by Michielsens et al. (2021) ended here (April 2020). The search strategy was based on the strategy of Michielsens et al.; terms on psoriasis, all available biologic therapies, and verbs associated with DR were added (Supplemental Appendix S1). Titles and abstracts were screened by two reviewers (CvR and JvdR), and one reviewer (CvR) assessed full articles on the inclusion and exclusion criteria. Discrepancies were resolved by a second reviewer (JvdR) and, if necessary, by a third reviewer (EdJ). All studies providing full-text original research data on the DR of biologics in adults with plaque psoriasis were included. The definition of DR included the administration of a lower dose per administration or injection interval prolongation. Prior to DR, the initial treatment had to be in accordance with the registered dose of the biologic. Some biologics have two registered doses (e.g., adalimumab); changing the higher registered dose to a lower registered dose was not considered DR. However, one exception was made regarding the IL-12/23 inhibitor ustekinumab since its doses are weight-dependent. Accordingly, if a patient with a weight >100 kg reduced the dose from 90 mg to 45 mg, this was considered DR. Data extraction was performed by CvR. To provide an overview of the total body of evidence on DR strategies, the predesigned charting form from the previous review (Michielsens et al., 2021) was complemented with data from the present review (Supplemental Appendix S2). This charting form included the following data: study characteristics, eligibility criteria for DR, strategy of DR, DR outcomes (% of patients with successful lower doses, Psoriasis Area and Severity Index [PASI], Physician Global Assessment [PGA], Dermatology Life Quality Index [DLQI], % of relapses, and % of flares), and retreatment strategy in the case of relapse after DR and its effectiveness. Data on safety, effect on the quality of life

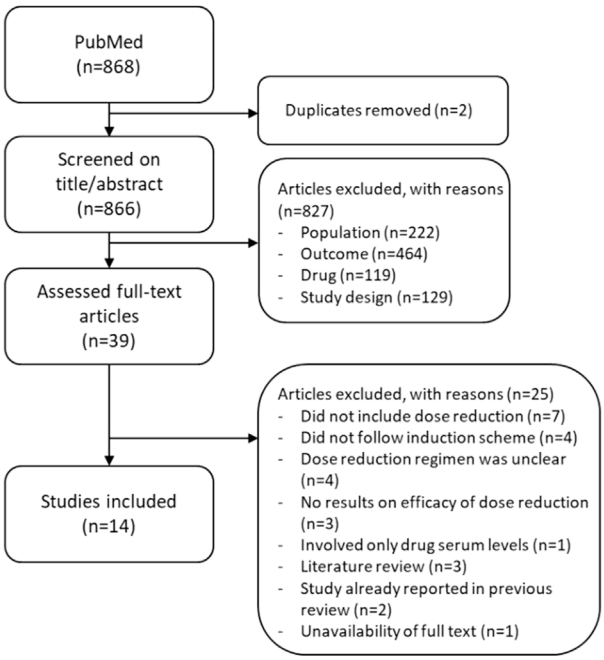

FIGURE 1
Flowchart of the study selection of 868 studies found between 1 January 2020 and 5 July 2023.

(QoL), costs, and implementation were also extracted when described. All the data were summarized narratively.

3 Results

The studies included in the previous review by Michielsens et al. are shown in detail in Supplemental Appendix S2. In summary, this previous review reported the results of 19 studies on the effectiveness of DR strategies of biologics for psoriasis, of which 14 studies investigated the DR of adalimumab, 9 of etanercept, 5 of infliximab, 8 of ustekinumab, 1 of secukinumab, and 1 of brodalumab (Michielsens et al., 2021). The definition of low disease activity as a measure of DR eligibility widely varied among the included studies, and DR strategies were also heterogeneous. Evidence of regaining response after relapse due to DR was scarce, but restored remission was shown. The studies did not show a significant effect of DR on the occurrence of safety issues. Some studies reported on cost savings, but a formal cost-effectiveness analysis could not be identified at that time (Michielsens et al., 2021).

3.1 Included new studies

A total of 868 studies were screened for this updated review on title and abstract, of which 39 unique articles were selected for full-text screening. Eventually, 14 new articles were included (Figure 1). These articles involved four studies testing DR strategies (Atalay et al., 2021; Atalay et al., 2022b; Di Altobrando et al., 2022; Herranz-Pinto et al., 2023), one specifically focusing on the effectiveness of returning to standard dosages when DR failed (van der Schoot et al., 2022a), two addressing the safety of DR (Atalay et al., 2022a; Benzaquen et al., 2022), one evaluating the cost-effectiveness of DR (Atalay et al., 2020b), and six investigating the implementation and uptake of DR (Aubert et al., 2022; van der Schoot et al., 2022b; van Muijen et al., 2022; Aubert et al., 2023; van der Schoot et al., 2023a; van der Schoot et al., 2023b). All four studies testing DR strategies were cohort studies, of which three were prospective and one was retrospective. One study was a 1-year extension of a sub-cohort of the prospective CONDOR trial (Atalay et al., 2022b). The CONDOR trial is a multi-centric, randomized clinical trial (RCT) on the DR of adalimumab, etanercept, and ustekinumab, which was already highlighted in the previous scoping review by Michielsens et al. (Atalay et al., 2020a; Michielsens et al., 2021; Atalay et al., 2022b). The sub-cohort in the 1-year extension study comprised a total of 88 patients (single center) using either a reduced dose (N = 44/88) or standard dose (N = 44/88) of adalimumab, etanercept, or ustekinumab at the end of the CONDOR trial (Atalay et al., 2022b). The second study comprised a prospective observational cohort study, with a total of 80 patients using a one-step DR strategy of either adalimumab, etanercept, or ustekinumab in daily practice, who were observed for an average of 1 year (Atalay et al., 2021). The third prospective cohort study was by Di Altobrando et al. (2022), in which a total of 199 patients started a reduced dose (N = 96/199) or continued a standard dose (N = 103/199) of either adalimumab, etanercept, infliximab, or ustekinumab for maximal of ±102 months. Herranz-Pinto et al. (2023) performed a retrospective cohort study with a total of 69 patients, who started a reduced dose (N = 45/64) or continued the standard dose (N = 24/69) of guselkumab and were observed for a maximum of 90 weeks. Some studies were found in which a DR strategy of secukinumab, ixekizumab, brodalumab, and tildrakizumab was tested but were eventually excluded due to an uncertainty of which DR strategies were studied, whether an induction scheme was followed or not, or because DR was applied from the start of biologic use, or because results did not include effect measurements. The most frequently studied biologics were still first-generation biologics (adalimumab, etanercept, and ustekinumab). Six of the seven IL-17 and IL-23 inhibitors were mainly addressed in studies regarding costs, uptake, and implementation of DR and are described later.

3.2 Dose reduction strategies

3.2.1 Eligibility criteria for dose reduction

The eligibility criteria used to start DR in the four pre-mentioned studies were roughly divided into two types: (i) the treatment duration of the biologic used in the standard dose prior to DR and (ii) the effectiveness of the biologic used in the standard dose at the moment of considering DR. In the 4 included studies, the treatment duration prior to DR ranged from ≥150 days (Herranz-Pinto et al., 2023) to ≥6 months (Atalay et al., 2021; Atalay et al., 2022b) to ≥1 year prior to DR (Di Altobrando et al., 2022). The effectiveness of the biologic used in the standard dose was determined by scoring the disease activity or state of clinical remission by using the absolute and/or relative PASI. The precise cut-off values of PASI varied between studies; however, all studies required low disease activity or a specific state of clinical remission for a certain period. Di Altobrando et al. (2022) chose a relative PASI 75–100 for ≥1 year, Herranz-Pinto et al. (2023) chose a complete response after 12 weeks (relative PASI 100), and both studies by Atalay et al. (2021) and Atalay et al. (2022b) used a PASI ≤5 for ≥6 months. Only the studies by Atalay et al. (2021); Atalay et al. (2022b) included the quality of life as an additional eligibility criterion, which was defined as a DLQI score of 5 or lower. The previous review by Michielsens et al. (2021) showed similar criteria regarding the treatment duration prior to DR and the effectiveness of the biologic used. The treatment duration prior to DR ranged from 6 weeks to ≥1 year, although the majority maintained a period of ≥ 6 months. In addition to the absolute and/or relative PASI score, the PGA or clinicians' judgment was used to determine the effectiveness of the biologic used in the standard dose. Precise cut-off values also varied between studies, although all studies also required low disease activity or a certain state of clinical remission for a certain period of time ranging from a minimal of 6 weeks to ≥1 year. The CONDOR study was also the only study that used DLQI ≤ 5 as additional eligibility criteria (Atalay et al., 2020a). Only 2 of the 19 studies included in the previous review did not mention any eligibility criteria (Michielsens et al., 2021).

3.2.2 Dose reduction strategies

In all four newly included studies, the induction phase of the biologics according to the standard dose prior to DR was followed. All studies applied DR by interval prolongation (Table 1). In the 1-year extension study by Atalay et al. (2022b), DR was performed stepwise by interval prolongation in two steps. The first step consisted of 67% of the standard dose (adalimumab every

TABLE 1 Overview of all different dose reduction strategies used in the included studies testing dose reduction strategies by Michielsens et al. (2021) and the updated search. For each strategy, the references are shown as superscript.

Biologics		Standard dose	DR strategies	% of the standard dose
First generation				
TNF-α inhibitor	Adalimumab	40 mg Q2W	40 mg Q3W (Fotiadou et al., 2012; Lopez-Ferrer et al., 2013; Baniandres et al., 2015; Piaserico et al., 2016; Romero-Jimenez et al., 2016; Hansel et al., 2017; van Bezooijen et al., 2017; Atalay et al., 2020a; Atalay et al., 2021; Atalay et al., 2022b; Di Altobrando et al., 2022)	67%
			40 mg Q4W (Lopez-Ferrer et al., 2013; Taniguchi et al., 2013; Baniandres et al., 2015; Hansel et al., 2017; van Bezooijen et al., 2017; Lee et al., 2018; Atalay et al., 2020a; Atalay et al., 2022b)	50%
			40 mg Q6W (Baniandres et al., 2015)	33%
	Etanercept	50 mg QW	50 mg Q10D (Baniandres et al., 2015; Piaserico et al., 2016; Romero-Jimenez et al., 2016; Atalay et al., 2020a; Atalay et al., 2021; Atalay et al., 2022b; Di Altobrando et al., 2022)	70%
			50 mg Q14D (Baniandres et al., 2015; van Bezooijen et al., 2017; Atalay et al., 2020a; Atalay et al., 2022b)	50%
		25 mg 2x/W	25 mg QW (Baniandres et al., 2015)	50%
			25 mg Q10D (Baniandres et al., 2015)	35%
	Infliximab	5 mg/kg Q8W	5 mg/kg Q9W (Baniandres et al., 2015; Romero-Jimenez et al., 2016)	89%
			5 mg/kg Q10W (Bardazzi et al., 2016; Di Altobrando et al., 2022)	80%
			5 mg/kg Q11W (Baniandres et al., 2015)	73%
IL-12/ 23 inhibitor	Ustekinumab	Weight <100 kg 45 mg Q12W	45 mg Q13W (Baniandres et al., 2015; Romero-Jimenez et al., 2016)	92%
			45 mg Q14W (Baniandres et al., 2015; Di Altobrando et al., 2022)	86%
			45 mg Q16W (Blauvelt et al., 2017; van Bezooijen et al., 2017)	75%
			45 mg Q18W (Atalay et al., 2020a; Atalay et al., 2021; Atalay et al., 2022b)	67%
			45 mg Q20W (Blauvelt et al., 2017; van Bezooijen et al., 2017)	60%
			45 mg Q24W (Blauvelt et al., 2017; van Bezooijen et al., 2017; Atalay et al., 2020a; Atalay et al., 2022b)	50%
		Weight >100 kg 90 mg Q12W	90 mg Q16W (Blauvelt et al., 2017)	75%
			90 mg Q20W (Blauvelt et al., 2017)	60%
			90 mg Q24W (Blauvelt et al., 2017)	50%
			45 mg Q12W (van Bezooijen et al., 2017)	50% *
Newest generation				
IL-17 inhibitor	Secukinumab	300 mg Q4W	300 mg Q6W (Reich et al., 2020)	67%
	Brodalumab	210 mg Q2W	140 mg Q2W (Lebwohl et al., 2015)	67% *
			140 mg Q4W (Lebwohl et al., 2015)	50%
			140 mg Q8W (Lebwohl et al., 2015)	25%
IL-23 inhibitor	Guselkumab	100 mg Q8W	100 mg Q11W (Herranz-Pinto et al., 2023)	71%
			100 mg Q17W (Herranz-Pinto et al., 2023)	48%
			100 mg Q27W (Herranz-Pinto et al., 2023)	29%

DR, dose reduction; TNF, tumor necrosis factor; IL, interleukin; mg, milligram; Q, every; W, weeks; D, days; for example, Q2W meant every 2 weeks. * DR by lowering administration dose per administration.

3 weeks, etanercept every 10 days, and ustekinumab every 18 weeks), and the second step involved 50% of the standard dose (adalimumab every 4 weeks, etanercept every 2 weeks, and ustekinumab every 24 weeks) (Atalay et al., 2022b). In their other cohort study, DR was performed by fixed interval prolongation in one step: 67% of the standard dose (adalimumab every 3 weeks,

etanercept every 10 days, and ustekinumab every 18 weeks) (Atalay et al., 2021). In the study by Di Altobrando et al. (2022), DR was also performed by fixed interval prolongation in one step but with different percentages of the standard dose ranging from 67% (adalimumab every 3 weeks and etanercept every 10 days) to 80% (infliximab every 10 weeks) to 86% (ustekinumab every 14 weeks). In the study by Herranz-Pinto et al. (2023), DR was performed by interval prolongation on-demand and showed that doses ranged from 73% (guselkumab every 11 weeks) to 47% (guselkumab every 17 weeks) to 30% (guselkumab every 27 weeks) of the standard dose. The studies included in the previous review applied DR by either interval prolongation or lowering the administration dose (Table 1) (Michielsens et al., 2021). However, Lebwohl et al. (2015) applied DR in both ways for brodalumab by increasing the interval in weeks while using 140 mg per administration instead of 210 mg. In addition, the study by van Bezooijen et al. (2017) was the only study that only lowered the administration dose by administering 45 mg of ustekinumab to a patient weighing >100 kg instead of 90 mg. All DR strategies used in the four included studies on DR strategy, complemented with the strategies used in the studies included in the previous review, are shown in Table 1. In summary, as shown in Table 1, the most frequently used strategies were either ±67% or ±50% of the standard dose of adalimumab, etanercept, ustekinumab, secukinumab, brodalumab, and guselkumab. Only studies involving infliximab did not go below 73% of the standard dose (Baniandres et al., 2015; Bardazzi et al., 2016; Romero-Jimenez et al., 2016; Di Altobrando et al., 2022). Only for brodalumab and guselkumab were lower DR strategies shown, i.e., 25% and 30% of the standard dose, respectively (Lebwohl et al., 2015; Herranz-Pinto et al., 2023). Similarly, Baniandres et al. (2015) applied a low DR of 33% and 35% of the standard dose in adalimumab and etanercept, respectively; however, this was done only in two patients for each biologic.

3.3 Effectiveness of dose reduction

The effectiveness of the DR strategies was investigated in the four pre-mentioned studies (Atalay et al., 2021; Atalay et al., 2022b; Di Altobrando et al., 2022; Herranz-Pinto et al., 2023). Three of the four studies included adalimumab, etanercept, and ustekinumab, of which one study also included infliximab. One study included guselkumab. An overview of the results is given in Supplemental Appendix S2. One of the 14 included studies specifically focused on the effectiveness of *retreatment* in the case of relapse after the DR of adalimumab, etanercept, and ustekinumab. Detailed summaries on the design and outcomes regarding the effectiveness of DR are given in Supplemental Appendix S3.

3.3.1 Atalay et al.—prospective cohort (N = 88) (1-year extension study of the randomized CONDOR trial) on adalimumab, etanercept, and ustekinumab

In the 1-year extension study of the CONDOR trial, a sub-cohort of a total of 88 patients was followed for another year after the end of the trial, resulting in a total follow-up of 2 years for this specific cohort (Atalay et al., 2022b). The sub-cohort comprised patients from one center who were initially randomized to a reduced dose (N = 44/88) or standard dose (usual care, UC) (N = 44/88) of adalimumab (DR N = 18; UC N = 17), etanercept (DR N = 11; UC N = 12), or ustekinumab (DR N = 15; UC N = 15) at the start of the CONDOR trial. The results were not specified per biologic but on a total study population level. At the end of the 1-year CONDOR trial, 59% of the patients initially randomized to DR (26/44 patients) were still on a low dose. At the end of the 1-year extension study (i.e., 2 years after CONDOR initiation), 69% of this group (18/26 patients) was still on a low dose (N = 7 used 67% of the standard dose and N = 11 used 50% of the standard dose). Over a total of 2 years of follow-up, 10 patients relapsed after DR, of which 80% (8/10 patients) regained response after retreatment with the previous effective dose (Atalay et al., 2022b).

3.3.2 Atalay et al.—prospective cohort (N = 80) (one-step DR strategy) on adalimumab, etanercept, and ustekinumab

In this prospective cohort study, a total of 80 patients who started with a one-step DR strategy of adalimumab (N = 42), etanercept (N = 16), or ustekinumab (N = 22) were followed for, on average, 1 year after the start of DR (Atalay et al., 2021). DR was performed by fixed interval prolongation to 67% of the standard dose. Of the total study population, 45% (36/80 patients) discontinued DR (discontinuation of DR split per biologic: adalimumab, 45% (19/42 patients); etanercept, 44% (7/16 patients); and ustekinumab, 46% (10/22 patients)). Over the total follow-up period, a total of 8 out of 80 patients (10%) relapsed after DR, of which 50% (N = 4) continued DR at their own request and 50% (N = 4) returned to the standard dose. Response was regained within 6 months for 100% of patients who continued DR and 75% of patients who returned to the standard dose (3/4 patients) (Atalay et al., 2021).

3.3.3 Di Altebrando et al.—prospective cohort (N = 199) on adalimumab, etanercept, infliximab, and ustekinumab

In this prospective cohort study, a total of 199 patients, of which 96 patients started with DR and 103 patients continued the standard dose (UC) of adalimumab (DR N = 47; UC N = 34), etanercept (DR N = 16; UC N = 25), infliximab (DR N = 21; UC N = 7), or ustekinumab (DR N = 12; UC N = 37), were followed for a maximum of ±102 months after the start of DR (Di Altobrando et al., 2022). The dose was reduced by fixed interval prolongation to 67% of the standard dose for adalimumab and etanercept, 80% for infliximab, and 86% for ustekinumab. During the follow-up, a total of 26 out of 96 patients (27%) on DR relapsed. For adalimumab DR, 36% (17/47 patients) relapsed; for etanercept DR, 6% (1/16 patients) relapsed; for infliximab DR, 24% (5/21 patients) relapsed; and for ustekinumab DR, 25% (3/12 patients) relapsed. Of all 26 relapsed patients, 96% (25/26 patients) regained their initial PASI score after retreatment with the standard dose (Di Altobrando et al., 2022).

3.3.4 Herranz-Pinto et al.—retrospective cohort (N = 69) on guselkumab

This retrospective cohort study included a total of 69 patients, of which 45 underwent an "on-demand" DR strategy of guselkumab (Herranz-Pinto et al., 2023). After an initial complete response, patients re-administered guselkumab only when their absolute PASI reached ≥1. The follow-up was 88 weeks. Patients were divided into

four groups: one standard dose group and three groups based on the % DR of the standard dose. The "blue group" had an average reduction of 29% (N = 24), the "orange group" had 52% (N = 10), and the "red group" had 71% (N = 11). All DR groups showed a significant decrease in PASI between weeks 11 and 20 compared to the baseline. After 1 year, drug survival curves showed a survival rate of 93.5% in the overall population (including patients on standard dose), 94.4% in the blue group, and 100% in the orange and red groups without significant differences between groups (p = 0.48) (Herranz-Pinto et al., 2023).

3.3.5 van der Schoot et al.,—prospective cohort study (N = 59) on the effectiveness of retreatment with adalimumab, etanercept, and ustekinumab

One prospective cohort study by van der Schoot et al. (2022a) specifically analyzed the effectiveness of retreatment with the standard dose in the case of relapse after DR in 59 patients using either adalimumab (N = 23), etanercept (N = 16), or ustekinumab (N = 20). A total of 40 out of 59 patients (68%) returned to the standard dose based on the protocol (PASI and/or DLQI >5) and 19/59 patients (32%) at their own request. After 1 year of retreatment with the standard dose, the absolute PASI was comparable to the PASI at the start of DR. The median PASI at the start of DR was 2.4 ([interquartile range (IQR) 1.5-3.0]) and the median difference with the PASI after 1 year of retreatment was 0.0 [(IQR −0.8; −1.5)] (van der Schoot et al., 2022a).

3.4 Quality of life

Three out of the four included studies testing DR strategies also reported on the QoL. Both studies by Atalay et al. (2021); Atalay et al. (2022b) included the QoL by including the DLQI score, in addition to PASI, in their eligibility criteria (DLQI ≤5), strategy, and as a measurement tool for relapses (DLQI >5) in patients using adalimumab, etanercept, or ustekinumab. In the 1-year extension study, the median (IQR) DLQI scores of the 26 patients who were still on a low dose of adalimumab, etanercept, or ustekinumab at the end of the 1-year CONDOR trial were 1.0 [0.0–3.0] at 12 months, 1.0 [1.0–3.0] at 15 months, 1.0 [0.3–2.0] at 18 months, 0.5 [0.0–1.8] at 21 months, and 1.0 [0.0–1.0] at 24 months (Atalay et al., 2022b). No significant differences in DLQI scores were found between patients on DR vs. the standard dose (Atalay et al., 2022b). In the one-step DR study, analyses on the QoL were performed within a sub-cohort of their original cohort, including patients who started DR ≥ 1 year ago (67/80 patients) (Atalay et al., 2021). At the baseline, 6 months, and 12 months, the median (IQR) DLQI scores were 0 [0–1], 0 [0–1.5], and 0.5 [0–2], respectively (Atalay et al., 2021). Di Altobrando et al. (2022) developed an unvalidated four-question questionnaire on patient-perceived satisfaction. The score could range from 5 to 20, with lower scores indicating less satisfaction. The questionnaire was filled out 3 months after the baseline by patients on DR. Of the patients on 40 mg adalimumab Q3W, 79% (37/47 patients) were completely or very satisfied with their reduced dose, 19% (9/47 patients) were quite satisfied, and 2% (1/47 patients) were unsatisfied. Furthermore, 77% (36/47 patients) felt more healed with their reduced dose (Di Altobrando et al., 2022). Of the patients on 50 mg etanercept Q10D, 63% (10/16 patients) were completely or very satisfied, 31% (5/16 patients) were quite satisfied, 6% (1/16 patients) were unsatisfied with their reduced dose, and 69% (11/16 patients) felt more healed (Di Altobrando et al., 2022). Of the patients on infliximab 5 mg/kg Q10W, 19% (4/21 patients) were completely or very satisfied, 81% (17/21 patients) were quite satisfied, no patients were unsatisfied with their reduced dose, and 76% (16/21 patients) felt more healed (Di Altobrando et al., 2022). Of the patients on 45 mg ustekinumab Q14W, 100% (12/12 patients) were completely or very satisfied with their reduced dose and 67% (8/12 patients) felt more healed (Di Altobrando et al., 2022). The previous review by Michielsens et al. (2021) reported the results of three studies on the QoL. All three studies included the DLQI score to measure the QoL. In the CONDOR trial, the median (IQR) DLQI was 1.0 (0.0–2.0) for patients on DR and 0.0 (0.0–2.0) on standard dose, with a mean difference of 0.8 (95% CI 0.3–1.3) after 1 year (Atalay et al., 2020a). Reich et al. (2020) showed in their RCT on secukinumab (300 mg Q6W vs. standard dose) a significant decrease in the DLQI score of 0.62 (95% CI 0.93–0.31, p = 0.0001) after 1 year in patients on DR compared to the standard dose. Fotiadou et al. (2012) showed in their retrospective cohort study on adalimumab a DLQI score of 0 for all patients who used adalimumab Q3W for 30 months (10/14 patients).

3.5 Safety

Two out of the 14 included studies focused specifically on the safety of DR in the context of antidrug–antibody (ADA) development in patients on DR. Benzaquen et al. (2022) analyzed retrospectively measured serum drug levels and ADA levels of the past 11 years in the blood of patients on DR of adalimumab (Q3W/Q4W) (N = 7). They showed median serum trough levels of 4.7 μg/mL (range 1.9–12.5) after a median period of 18 months of DR. During the 11 years of DR, no patient had developed relevant ADAs against adalimumab; ADA levels remained <10 μg/ml (Benzaquen et al., 2022). Atalay et al. (2022a) measured serum drug levels and ADA levels in the blood samples from the study population of the CONDOR trial (N = 118), which were collected during the trial. For adalimumab, etanercept, and ustekinumab, serum trough levels significantly decreased as intervals were prolonged. No significant differences in detectable ADA levels between DR and the standard dose of adalimumab were found; as for ustekinumab, ADAs were present in neither the DR nor the standard dose (Atalay et al., 2022a). The four studies on DR strategies also reported safety in terms of adverse or serious adverse events (AEs or SAEs). In the 1-year extension study, 1/26 patients on DR (4%) and 5/62 patients on the standard dose (8%) (N = 44 on the standard dose and N = 18 who returned to the standard dose before the start of the extension phase) reported musculoskeletal complaints (Atalay et al., 2022b). One patient, known to have had a previous episode of arthritis, was newly diagnosed with psoriatic arthritis during DR. One SAE in the DR group (in N = 1) and 12 SAEs in the standard dose group (in N = 5) were reported, but no hospital admissions due to exacerbations took place, and no SAEs were deemed causally related to DR (Atalay et al., 2022b). In the one-step DR study, DR was discontinued due to joint complaints in 2/36 patients (6%); no SAEs related to DR were reported (Atalay et al., 2021). Di Altobrando et al. (2022) mentioned that DR did not

result in an increase in AEs. Herranz-Pinto et al. (2023) reported no SAEs related to DR. The previous review by Michielsens et al. (2021) showed the results of six studies on safety. One of these studies reported on the incidence of ADA development in patients on ustekinumab Q24W vs. standard dose and also showed no differences (Blauvelt et al., 2017). Five out of 6 studies showed comparable rates of AEs and/or SAEs between DR and standard dose after a maximal follow-up of 96 weeks (Michielsens et al., 2021). Only in the CONDOR trial was a higher rate of general non-specific musculoskeletal complaints in patients on DR vs. the standard dose reported (rate ratio 4.92; 95% CI 2.04–11.87; $p < 0.001$) (Atalay et al., 2020a). However, none of the studies in the previous review reported safety issues causally related to DR (Michielsens et al., 2021).

3.6 Costs

One out of the 14 included studies was specifically about the costs associated with DR. A health-economic evaluation was performed by a cost-utility analysis (CUA) based on CONDOR trial data (Atalay et al., 2020b). The CUA showed a mean difference in the quality-adjusted life years (QALYs; calculated based on specific answers of the Short Form Health Survey (SF-36)) of −0.02 (95th percentile −0.06 to 0.02) and costs of -€3,820 (95th percentile -€3,099 to -€4,509) per patient over 12 months between DR and the standard dose (Atalay et al., 2020b). Two out of the four included studies on DR strategies reported on cost savings. In the one-step DR study by Atalay et al. (2021), cost savings for the 67 patients who started DR ≥1 year ago were analyzed and reported per biologic and for the total DR group. The mean cost savings per patient were €2,919.04 for adalimumab Q3W (N = 37), €1,540.16 for etanercept Q10D (N = 14), €1,579.98 for ustekinumab 45 mg Q18W, and €2,456.29 for 90 mg Q18W (N = 16). After 1 year, absolute cost savings of the total DR group were €159,228.16 compared to the standard dose, representing a mean reduction of 22.7% (Atalay et al., 2021). Di Altobrando et al. (2022) reported cost savings per biologic (€/year/patient on DR): €3,740.65 for adalimumab Q3W (N = 30), €3,489.90 for etanercept Q10D (N = 15), €1,885.80 for infliximab Q10W (N = 16) (based on an average patient of 70 kg with 5 mg/kg), and €1,596.20 for ustekinumab Q14W (N = 9). The previous review by Michielsens et al. (2021) mentioned that cost savings as a result of DR were described in six studies and showed results from five studies. All studies showed cost savings of hundreds to thousands of euros annually when the DR was applied compared to the standard dose (Michielsens et al., 2021).

3.7 Uptake and implementation of dose reduction

A total of 6 out of the 14 included studies were specifically focused on the implementation and uptake of DR (Aubert et al., 2022; van der Schoot et al., 2022b; van Muijen et al., 2022; Aubert et al., 2023; van der Schoot et al., 2023a; van der Schoot et al., 2023b). These studies mostly evaluated patients' or healthcare providers' experienced barriers or facilitators toward DR through surveys and/or interviews and also included the results of a cohort study, a national consensus study, and an implementation study of a DR protocol. The design and outcomes of these studies are described in detail in Supplemental Appendix S4.

3.7.1 Aubert et al.—report on the uptake of DR in a prospective cohort study (PsoBioTeq registry) (N = 850)

This research study reported on the results of 850 patients in the French prospective PsoBioTeq registry cohort (Aubert et al., 2023). All patients were in remission or had low disease activity (R/LDA) (PASI ≤3 or PGA ≤1 and/or no psoriatic lesions during ≥2 consecutive visits). A total of 93 out of 850 patients started DR by either reducing the dose in mg (N = 6/93; 6%) or interval prolongation (N = 87/93; 94%). The included biologics were TNF-α inhibitors (N = 63/93; 68%), the IL-12/23 inhibitor (N = 22/93; 24%), and IL-17 inhibitors (N = 8/93; 9%). Multivariate analysis showed that the interval from the start of biologic treatment to R/LDA was predictive of starting DR. In particular, patients using TNF-α inhibitors showed that the more rapidly remission was achieved, the sooner DR could be applied, compared to patients using IL-12/23 or IL-17 inhibitors. Age, severity, or type of psoriasis showed no significant impact (Aubert et al., 2023).

3.7.2 van der Schoot et al.—qualitative interviews among psoriasis patients (N = 15)

Qualitative interviews with a total of 15 psoriasis patients using biologics were held about their experience, beliefs, and needs regarding DR (van der Schoot et al., 2023b). The interviews revealed patients' barriers and facilitators to DR, divided into seven different themes: (1) disease control (the higher the effort needed to reach a low disease activity, the more the patients felt a barrier to start DR); (2) attitudes toward medication and DR (e.g., absence of side effects was a barrier as patients could not see advantages in DR; experiencing side effects was a facilitator, as well as confidence in DR, less medication use, and unpleasant injections); (3) healthcare access and organizational aspects (e.g., quick access to healthcare in the case of relapse was a facilitator of DR); (4) cost reduction (contributing to reduced societal healthcare costs was a facilitator); (5) information needs (adequate information on DR rationale, evidence, expected effectiveness, potential risks, and treatment options in the case of relapse was a facilitator); (6) social aspects (providing patients space to discuss DR with relatives was a facilitator); and (7) decision-making (involving patients in decision-making and the possibility to address patients' physical and mental health before and during DR were mentioned as a facilitator) (van der Schoot et al., 2023b).

3.7.3 van Muijen et al.—survey on the uptake of DR among dermatologists worldwide (N = 53)

This survey on the uptake of DR was distributed among dermatologists worldwide in 2020 via the International Psoriasis Council and included questions regarding eligibility criteria, strategies, and barriers for applying biologic DR in psoriasis (van Muijen et al., 2022). Fifty-three out of 114 invitees could be included, and 37/53 dermatologists (70%) applied DR. For all IL-17 and IL-23 inhibitors (excluding bimekizumab) DR was applied and most frequently for secukinumab (65%). Also, for the TNF-α inhibitors and IL-12/23 inhibitor DR was applied. The most frequently used

criteria for applying DR by the 37/53 "DR-applying dermatologists" were starting DR at the patient's request (27%), a disease activity score of the absolute PASI or BSA of ≤1 or ≤2 or PGA ≤1 (46%), a minimal treatment duration of ≥1 year (65%), and a stable low disease activity for ≥1 year (41%). DR was most frequently performed in two steps comparable to the strategies shown in Table 1: first, 67% of the standard dose and second, 50%. Additionally, infliximab was not reduced beyond 80% of the standard dose, as shown in Table 1. The discontinuation of DR was most frequently determined by disease activity scores (70%), followed by a combination of disease activity and patients' requests (24%), solely on patients' requests (3%) or based on "nothing particular" (3%). In 14/26 dermatologists who used disease activity scores (54%), the dose would be re-increased when the PASI or BSA ≥3; in 13/37 "DR-applying dermatologists" (35%), a clinical evaluation of "moderate disease activity" also resulted in re-increasing the dose, in addition to the use of disease activity scores (van Muijen et al., 2022). Reported barriers for DR by both users and non-users of DR included a lack of scientific evidence on safety and efficacy, lack of guidelines, limited experience with DR and/or prescription of (the newest generation) biologics, time constraints, lack of (technical) support, fear of antibody formation, believing that patients are unwilling to apply DR, and thoughts that biological cost-reducing belongs to pharmaceuticals instead of clinicians. The most frequently reported facilitator to apply DR was cost savings (N = 32/37 "DR-applying dermatologists; " 86%), safety/fewer side effects (43%), patients' requests (41%), and prevention of unnecessary high dosages (5%) (van Muijen et al., 2022).

3.7.4 Aubert et al.,—survey on the uptake of DR among French dermatologists of the Resopso study group (N = 54)

This survey on the uptake of biologic DR, i.e., investigating strategies used in daily practice, was performed among French dermatologists of the Resopso "Groupe d'Étude Multicentrique" (GEM) study group (Aubert et al., 2022), a community of ≥1,200 French dermatologists and ≥600 other health professionals involved in chronic inflammatory dermatoses (http://resopso.fr) (Resopso). According to the responding dermatologists (N = 54; 5% of the total group), 3 different treatment strategies were adopted in patients with "clear" or "almost clear" psoriasis: stop biologic, DR by interval prolongation, and DR by lowering the administration dose (Aubert et al., 2022). Interval prolongation was proposed as a possible strategy for three out of four IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab), one IL-23 inhibitor (guselkumab), all TNF-α inhibitors, and the IL-12/23 inhibitor. Among the 54 dermatologists, interval prolongation was "most often" (46%) or "always" applied (7%) and stopping biologic use was "often" applied (53%). The most frequently used criteria defining disease activity (clear/almost clear) were DLQI ≤3 (54%), PASI ≤3 (48%), PGA ≤1 (48%), BSA ≤1% (46%), and relative PASI 90 (46%). Different strategies were adopted in the case of relapse after DR: returning to the standard dose (57%), returning to the previous effective dose (15%), applying the induction scheme again (18%), adding another systemic treatment like methotrexate (3%), switch of biologic (2%), or other (5%) (Aubert et al., 2022). Responding dermatologists mentioned the following decision factors that were relevant for applying DR: patient preference (65%), molecule type (54%), low disease activity (50%), immunogenicity risk (50%), age at onset (39%), psoriatic arthritis (39%), biologic non-naivety (35%), risk of loss of efficacy in the case of relapse (35%), risk of relapse (20%), and patient's age (17%) (Aubert et al., 2022).

3.7.5 van der schoot et al.—national consensus study on DR (N = 27)

An online Delphi procedure (eDelphi) was performed in the Netherlands to achieve consensus among Dutch dermatologists, recruited via the Dutch Association for Dermatology and Venerology, on criteria for biologic DR; 27/850 dermatologists participated (van der Schoot et al., 2022b). Consensus was reached on the following eligibility criteria: a minimal treatment duration of and minimal low disease activity for 6 months; PASI ≤5 and/or PGA 0-2 and DLQI ≤5 at the start of DR; a rheumatologist needs to be consulted prior to DR in the case of psoriatic arthritis; outpatient clinic visits should not become more frequent when DR is applied; and DR (of IL-17 and IL-23 inhibitors) can be considered in individual patients while awaiting more scientific evidence. Consensus was reached on the following DR (dis)continuation criteria: continue DR when PASI ≤5 and/or PGA 0–2 and DLQI ≤5; return to the standard or previous effective dose when PASI >5/PGA >2/DLQI >5 or at patients' request or when considered necessary by the dermatologists; and consider further DR after 3 months of DR for biologics with a standard interval of <8 weeks and after 6 months for biologics with a standard interval of ≥8 weeks. Regarding the DR strategy, consensus was reached for a two-step DR of first 67% and second 50% of the standard dose, specifically for adalimumab and etanercept, but smaller steps for ustekinumab (van der Schoot et al., 2022b).

3.7.6 van der Schoot et al.—implementation study of a DR protocol in three Dutch hospitals

An implementation study was performed in three Dutch hospitals evaluating the implementation process of a DR protocol for adalimumab, etanercept, and ustekinumab (van der Schoot et al., 2023a). Healthcare providers experienced the following barriers: lack of awareness, knowledge, routine, and experience with DR, time constraints, and lack of (technical) support. Additionally, healthcare providers mentioned the following facilitators: uptake of DR into guidelines, feasible protocols, available additional staff for the support of both physicians and patients to educate and/or support in clinical measurements, involving patients in decision-making, and providing IT solutions regarding automated disease activity scoring systems and decision aids in the electronic health record (van der Schoot et al., 2023a).

4 Current research gaps and potential developments

The literature on the newest generation of biologics is scarce, and a substantial number of studies were excluded based on the lack of information needed to compare studies and evaluate DR strategies. For instance, a description of DR strategies and exact

dosing schedules was often missing. Improving reporting standards for DR studies would, therefore, be highly valuable. The effectiveness of DR strategies was sometimes not described, but it is essential to evaluate the added value of such interventions. Moreover, study populations are usually small, which makes drawing conclusions more difficult and the results less generalizable. It was interesting that 2 out of the 39 studies performed a DR strategy, which was not explicitly included in the search terms. Sanz-Gil et al. (2020) performed a retrospective cohort study on individualized dosing of the self-administration of biologics in patients with plaque psoriasis. They showed that individualization of dosages according to patients' needs and their responses resulted in injection interval prolongation but in a way that patients were more in the lead when they thought it was necessary to inject biologics. In most cases, this strategy resulted in an improvement in the PASI score (Sanz-Gil et al., 2020). However, this study was excluded after reading the full text due to a lack of clear effectiveness measurements. Herranz-Pinto et al. (2023) performed a similar DR strategy as patients used guselkumab on-demand, although patients re-administered guselkumab only when the absolute PASI reached ≥1, as previously shown. Gisondi et al. (2022) performed a prospective interventional study on the as-needed administration of risankizumab in 64 patients with plaque psoriasis and showed that patients maintained a PASI < 1 up to 38 weeks after injection. These studies showed that an as-needed DR strategy could also be a promising intervention. Therefore, administration as needed might be a potential development for biologic DR in plaque psoriasis, but a research gap still exists in this topic.

5 Discussion

This review provides an overview of the latest literature on biologic DR in plaque psoriasis, of all biologics including the newest generation of biologics and uptake and implementation of DR as new aspects, updating a previous scoping review on biologic DR published in 2021 (Michielsens et al., 2021). Reviewing literature published between 2020 and July 2023 showed that studies on the (cost-)effectiveness and/or safety of biologic DR in psoriasis are still scarce, especially regarding the newest generation biologics IL-17 and IL-23 inhibitors. Only one study on the DR strategy included an IL-23 inhibitor: guselkumab (Herranz-Pinto et al., 2023). Almost all IL-17 and IL-23 inhibitors were included in studies on the uptake and implementation of DR. In total, 14 articles were included (Atalay et al., 2020b; Atalay et al., 2021; Atalay et al., 2022a; Aubert et al., 2022; van der Schoot et al., 2022a; Atalay et al., 2022b; Benzaquen et al., 2022; van der Schoot et al., 2022b; Di Altobrando et al., 2022; van Muijen et al., 2022; Aubert et al., 2023; van der Schoot et al., 2023a; van der Schoot et al., 2023b; Herranz-Pinto et al., 2023). Multiple studies were excluded due to uncertainty in the DR strategy studied, induction scheme, or absence of effect measurements, and specifically, cost studies regarding IL-17 and IL-23 inhibitors did not include DR. Considering the studies on DR strategies, the eligibility criteria for DR mainly included biologic use for ≥6 months, a stable low disease activity from ≥6 months to ≥1 year, determined by an absolute or relative PASI (PASI ≤3/≤5/PASI 75–100) and/or DLQI ≤3/≤5, or BSA ≤1/≤2, or PGA ≤1/0-2 during a period ranging from 12 weeks to ≥1 year (Atalay et al., 2021; Aubert et al., 2022; Atalay et al., 2022b; van der Schoot et al., 2022b; Di Altobrando et al., 2022; van Muijen et al., 2022; Herranz-Pinto et al., 2023). DR was most frequently performed by interval prolongation in two steps: first, 67% of the standard dose, and second, 50% (see also Table 1). The study on DR of guselkumab showed that patients in all DR groups using guselkumab 100 mg Q11W or Q17W or Q27W, had a significant decrease in the PASI between weeks 11 and 20 after the start of DR compared to the baseline (Herranz-Pinto et al., 2023). The other studies on DR strategies showed no significant differences in effectiveness between patients on DR and the standard dose, especially for adalimumab, etanercept, infliximab, and ustekinumab (Atalay et al., 2021; Atalay et al., 2022b; Di Altobrando et al., 2022). In general, in the case of a relapse after DR, retreatment with the standard dose resulted in comparable disease activity as before the start of DR (Atalay et al., 2021; van der Schoot et al., 2022a; Atalay et al., 2022b; Di Altobrando et al., 2022). Regarding AEs and/or SAEs, no differences were found between patients on DR and the standard dose. Some studies even showed less or no AEs/SAEs in DR compared to the standard dose (Atalay et al., 2022b; Di Altobrando et al., 2022), and there were no signs of increased ADA development for adalimumab or ustekinumab (Atalay et al., 2022a; Benzaquen et al., 2022). No safety data on the newest biologics were published. Three studies reported on cost savings; these data were also mainly based on the DR of the first-generation biologics (Atalay et al., 2020b; Atalay et al., 2021; Di Altobrando et al., 2022). Regarding the uptake and implementation of DR, barriers and facilitators were identified that are important to take into account when implementing DR in practice (Aubert et al., 2022; van der Schoot et al., 2022b; van Muijen et al., 2022; Aubert et al., 2023; van der Schoot et al., 2023a; van der Schoot et al., 2023b). This review revealed the variety of DR strategies and showed the large body of evidence on the uptake and implementation of DR. Taking into account the most important facilitators (e.g., adequate information for patients and clear guidelines for dermatologists), as well as finding solutions for substantial barriers (time constraints and lack of support), is crucial. This review also identified potential developments for future research as some recent studies performed dose reduction by administration as needed and also showed promising results. Additionally, as mentioned before, some studies tested a DR strategy in which they reduced the dose from the start of biologics instead of following the induction scheme and also showed that this could be a promising intervention. However, these strategies were outside the scope of this review but might be a topic of added value for future studies. A limitation is that the search included only English-language articles.

The total body of evidence on DR strategies mainly comprised observational studies and RCTs were scarce with underrepresentation of the newest generation biologics. Additionally, a relatively large number of the newly included studies were performed or coordinated by the same study group/center. The diversity of studies could hamper the generalizability of results on the effectiveness, safety, and applicability of DR in different healthcare systems.

In summary, DR studies on TNF-α inhibitors and IL-12/23 inhibitor and several studies on some of the earlier IL-17

inhibitors and the IL-23 inhibitor guselkumab, robustly showed good clinical effectiveness and safety of various DR strategies, as well as the potential for substantial cost-savings. However, the literature on DR strategies of the newest generation of biologics remains scarce, and future research on DR strategies of IL-17 and IL-23 inhibitors remains necessary to complement guidelines on DR as guidelines are critical for DR implementation. Studies on the uptake and implementation of DR of almost all biologics of the first- and newest generation were prevalent, and this review provides an overview of facilitators and barriers for implementing DR. We believe that the implementation of DR in practice can be more successful when taking into account these important factors in implementation strategies.

Author contributions

CvR: conceptualization, formal analysis, investigation, methodology, project administration, supervision, visualization, writing–original draft, and writing–review and editing. CM: writing–review and editing and conceptualization. MvM: writing–review and editing and conceptualization. LvS: writing–review and editing. JvR: conceptualization, investigation, methodology, supervision, writing–review and editing, and formal analysis. EJ: conceptualization, investigation, methodology, supervision, writing–review and editing, and formal analysis.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

MvM carried out clinical trials for AbbVie, Celgene, Janssen, and Novartis and received a speaking fee from Janssen. All funding is not personal but goes to the independent Research Fund of the Department of Dermatology of the Radboud University Medical Centre, Nijmegen (Radboudumc), Netherlands. LvS carried out clinical trials for Almirall, Janssen, and Novartis. All funding is not personal but goes to the independent Research Fund of the Department of Dermatology of the Radboud University Medical Centre, Nijmegen, Netherlands. JvR carried out clinical trials for AbbVie, Celgene, and Janssen and received speaking fees/attended advisory boards from AbbVie, Janssen, BMS, Almirall, Leo Pharma, Novartis, UCB, and Eli Lilly and reimbursement for attending a symposium from Janssen, Pfizer, Celgene, and AbbVie. All funding is not personal but goes to the independent research fund of the Department of Dermatology of Radboudumc, Nijmegen, Netherlands. EJ received research grants from the independent research fund of the Department of Dermatology of Radboudumc, Nijmegen, Netherlands, from AbbVie, BMS, Janssen, Leo Pharma, Novartis, and UCB for research on psoriasis and acted as a consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis or eczema, including AbbVie, Amgen, Almirall, Celgene, Galapagos, Janssen, Eli Lilly, Novartis, Leo Pharma, Sanofi, and UCB. All funding is not personal but goes to the independent research fund of the Department of Dermatology of Radboudumc, Nijmegen, Netherlands.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1369805/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 10 June 2024
DOI 10.3389/fphar.2024.1256992

OPEN ACCESS

EDITED BY
Bettina Ryll,
Melanoma Patient Network Europe, Sweden

REVIEWED BY
Dongzhe Hong,
Brigham and Women's Hospital and Harvard Medical School, United States
Alberto Pavan,
Azienda ULSS 3 Serenissima, Italy

*CORRESPONDENCE
Sheng Han,
hansheng@bjmu.edu.cn
Duoduo Li,
tarako@163.com

RECEIVED 11 July 2023
ACCEPTED 27 May 2024
PUBLISHED 10 June 2024

CITATION
Gan Y, Shi F, Zhu H, Li H, Han S and Li D (2024), Cost-effectiveness of durvalumab plus tremelimumab in combination with chemotherapy for the treatment of metastatic non-small-cell lung cancer from the US healthcare sector's and societal perspectives. *Front. Pharmacol.* 15:1256992. doi: 10.3389/fphar.2024.1256992

Cost-effectiveness of durvalumab plus tremelimumab in combination with chemotherapy for the treatment of metastatic non-small-cell lung cancer from the US healthcare sector's and societal perspectives

Yena Gan[1], Fenghao Shi[2,3], He Zhu[2,3], Huangqianyu Li[2,3], Sheng Han[2,3]* and Duoduo Li[1]*

[1]Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [2]International Research Center for Medicinal Administration, Peking University, Beijing, China, [3]School of Pharmaceutical Sciences, Peking University, Beijing, China

Purpose: Metastatic non-small cell lung cancer (mNSCLC) has a high incidence rate, and economic burdens to patients, healthcare systems, and societies. Durvalumab plus tremelimumab and chemotherapy (T+D+CT) is a novel therapeutic strategy for mNSCLC, which demonstrated promising efficacy in a phase-3 randomized clinical trial, but its economic value remains unclear.

Methods: This economic evaluation used a hypothetical cohort of patients with mNSCLC, with characteristics mirroring those of the participants in the POSEIDON trial. Several partitioned survival models were constructed to estimate 15-year costs and health outcomes associated with the T+D+CT, durvalumab plus chemotherapy (D+CT) and chemotherapy alone (CT) strategies, discounting costs and effectiveness at 3% annually. Costs were in 2023 US dollars. Data were derived from the POSEIDON trial and published literature. Deterministic and probabilistic sensitivity analyses were performed to assess the uncertainty of input parameters and study generalizability. The analysis was designed and conducted from September 2022 to March 2023. To evaluate the cost-effectiveness of T+D+CT, compared with CT and D+CT, for mNSCLC from the perspectives of the US healthcare sector and society.

Findings: From the healthcare sector's perspective, the T+D+CT yielded an additional 0.09 QALYs at an increased cost of $7,108 compared with CT,

Abbreviations: AWP, average wholesale price; BSC, best supportive care; CMS, Centers for Medicare and Medicaid Services; CT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte associated protein 4; D+CT, durvalumab plus chemotherapy; DoR, duration of response; EVPI, expected value of perfect information; ICER, incremental cost-effectiveness ratio; mAb, monoclonal antibody; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer; OS, overall survival; OWSAs, one-way deterministic sensitivity analyses; PD, progressive disease; PD-L1/PD-1, programmed cell death ligand-1/programmed cell death-1; PFS, progression-free survival; PSAs, probabilistic sensitivity analyses; QALYs, quality-adjusted life years; QoL, quality of life; SDs, standard deviations; T+D+CT, durvalumab plus tremelimumab and chemotherapy; TRAEs, treatment-related adverse events; WTP, willingness-to-pay.

which resulted in an ICER of $82,501/QALY. The T+D+CT strategy yielded an additional 0.02 QALYs at an increased cost of $27,779 compared with the D+CT, which resulted in an ICER of $1,243,868/QALY. The economic results of T+D+CT vs. CT were most sensitive to the annual discount rate, subsequent immunotherapy cost, tremelimumab cost, palliative care and death cost, pemetrexed cost, and durvalumab cost. The T+D+CT strategy was considered cost-effective relative to CT in 59%–82% of model iterations against willingness-to-pay. thresholds of $100,000/QALY gained to $150,000/QALY gained. From the societal perspective, the T+D+CT can be considered as cost-effective as compared with CT or D+CT, independent of histology.

Implications: In this cost-effectiveness analysis, the T+D+CT strategy represented good value compared with CT for patients with mNSCLC from the perspectives of the healthcare sector and the society. This treatment strategy may be prioritized for mNSCLC patients at high risks of disease progression.

KEYWORDS

NSCLC, durvalumab, tremelimumab, healthcare, cost-effectiveness

1 Introduction

Non-small cell lung cancer (NSCLC) continues to be the leading cause of cancer-related mortality worldwide (Bray et al., 2018; Howlader et al., 2020; Siegel et al., 2022). Approximately one-half of patients have advanced or metastatic stage III disease at the time of diagnosis and many patients with local or regional disease subsequently develop recurrent or metastatic disease, the prognosis for which has been poor, with a five-year survival of approximately 9% (American Cancer Society, 2022). Immune checkpoint inhibitors targeting programmed cell death ligand-1/programmed cell death-1 (PD-L1/PD-1) have significantly improved patient outcomes and become the standard of care for metastatic NSCLC (mNSCLC) (Gandhi et al., 2018; Socinski et al., 2018).

Pembrolizumab, a selective, high-affinity human IgG1 monoclonal antibody (mAb) that blocks PD-L1 binding to PD-1 and CD80, is approved for the first-line monotherapy of patients with PD-L1-positive (tumor proportion score of 1% or more) tumors in the US (Azpicentral, 2022). Tremelimumab, a selective human IgG2 mAb that blocks cytotoxic T-lymphocyte associated protein 4 (CTLA-4) binding to B7.1 and B7.2 ligands, is approved for the treatment of patients with mNSCLC in combination with durvalumab and platinum-based chemotherapy in the US(Keam, 2023). POSEIDON (a phase III, global, randomized, open-label trial of tremelimumab plus durvalumab and chemotherapy (T+D+CT) or durvalumab plus chemotherapy (D+CT) vs. chemotherapy alone (CT) in patients with mNSCLC; [ClinicalTrials.gov identifier: NCT03164616]) clinical trial recently found that the combination of two immune checkpoint inhibitors, tremelimumab plus durvalumab (alongside chemotherapy), as the first-line treatment improved overall survival (OS) and progression-free survival (PFS) in patients with mNSCLC compared with CT, independent of PD-L1 expression (Johnson et al., 2023). It also found T+D+CT to be more efficacious than D+CT. However, T+D+CT resulted in a higher rate of treatment-related adverse events (TRAEs) than CT and D+CT.

Although T+D+CT showed promising results in treating mNSCLC, it remains unknown whether T+D+CT entails longer-term economic benefits. With the incidence rate of mNSCLC increasing and launch of highly priced anticancer agents, healthcare expenditure on novel anticancer treatments is rapidly expanding (Planchard et al., 2018; Chen et al., 2020; Horvath et al., 2020; Kasahun et al., 2020; Diao et al., 2022). This not only entails economic burden in itself but also can lead to compromised patient outcomes such as decreased quality of life (QoL) of patients who quit or delay treatment due to financial concerns (Courtney et al., 2021). This necessitates assessment of the cost-effectiveness of novel treatment regimens. In this study, we conducted a computer simulation model to assess the cost-effectiveness of T+D+CT compared with CT and D+CT as first-line treatment for patients with mNSCLC from the US healthcare sector and societal perspectives (Planchard et al., 2018; Chen et al., 2020; Horvath et al., 2020; Kasahun et al., 2020; Diao et al., 2022).

2 Methods

This economic evaluation used published clinical trial data and was therefore deemed exempt from institutional review board approval and informed consent by the institutional review board of Peking University, China. Economic analyses complied with the methodological guidelines set by the US Second Panel on Cost-Effectiveness in Health and Medicine and were reported in compliance with the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS) checklist (CHEERS, 2022).

2.1 Decision model

We constructed several partitioned survival models to simulate the cost-effectiveness of T+D+CT vs. CT and D+CT as the first-line therapy for mNSCLC patients from the perspectives of the US healthcare sector and the society. These models were constructed with a one-month cycle length and a horizon extending over 15 years, including three mutually exclusive health states: PFS, progressive disease (PD), and death (Figure 1). We constructed a hypothetical cohort of patients who had characteristics consistent

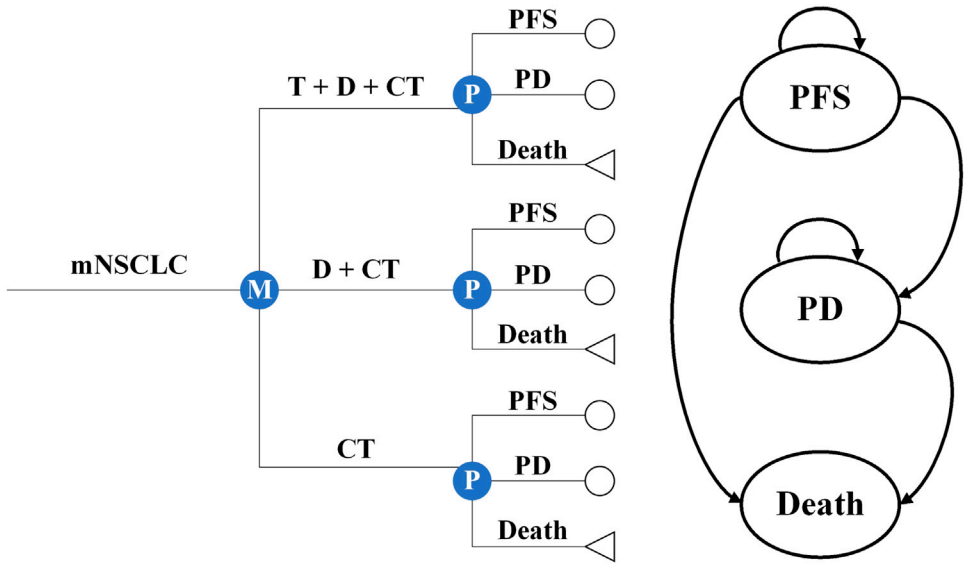

FIGURE 1
Microsimulation and decision tree model for different treatment regimens and health states. mNSCLC, metastatic non-small cell lung cancer; T+D+CT, tremelimumab plus durvalumab and chemotherapy; D+CT, durvalumab plus chemotherapy; CT, chemotherapy alone; PFS, progression-free disease; PD, progressive disease.

with those of the participants in the POSEIDON clinical trial (Supplementary eMethods). Patients entered the model in the PFS state; they could then remain in this state or experience TRAEs, PD, or death. The primary outcomes of the models were the direct costs associated with mNSCLC treatment and management and quality-adjusted life years (QALYs), which were used to derive the incremental cost-effectiveness ratio (ICER) and then compared with the willingness-to-pay (WTP) threshold of $100,000/QALY (Neumann et al., 2014). Both costs and QALYs were discounted at 3% annually (Sanders et al., 2016). All monetary terms were converted to 2023 US dollars using the Consumer Price Index. The Excel spreadsheet software (version 16, Microsoft) was used to build and run models. Data analyses were conducted from September 2022 to March 2023.

2.2 Treatment details

The POSEIDON clinical trial stratified patients by PD-L1 expression (tumor proportion score ≥50% or <50%) and randomized patients to receive T+D+CT, D+CT, or CT (Supplementary eMethods). All clinical data used in our primary cost-effectiveness analysis were obtained from the POSEIDON clinical trial. The base case models followed the POSEIDON trial protocol, in which patients received treatment with durvalumab or durvalumab-tremelimumab combination therapy until PD or unacceptable TRAEs, whichever occurred first. Per the POSEIDON protocol, certain patients could continue to receive durvalumab monotherapy after PD if they continued to receive benefit and met prespecified criteria. For patients who received five cycles of durvalumab-tremelimumab combination therapy and subsequently had PD during durvalumab monotherapy, they could receive retreatment with up to four additional cycles of tremelimumab alongside durvalumab. In accordance with the POSEIDON protocol, patients who were receiving upfront chemotherapy in our base case models also received treatment until PD, unacceptable TRAEs, or 18 weeks of treatment, whichever occurred first. In addition, per the POSEIDON protocol, patients with non-squamous histology who received cisplatin or carboplatin plus pemetrexed could receive pemetrexed maintenance therapy until PD or unacceptable TRAEs.

2.3 Model parameters

2.3.1 Model parameters

The probabilities for the partitioned states were derived from the reported Kaplan-Meier (K-M) curves of OS and PFS in the POSEIDON (Supplementary eMethods; Supplementary eFigure S1; Supplementary eTable S1). Of note, the trial only reported PFS data through 23 months and OS data through 44 months after the initiation of treatment. The following survivals were estimated using parametric survival functions (Supplementary eMethods; Supplementary eFigure S1).

2.3.2 Costs

We considered costs from both the healthcare sector's and societal perspectives. The formal healthcare costs consisted of costs attributable to drugs, management of TRAEs, imaging, best supportive care (BSC), radiotherapy, and palliative care and death. Drug costs were extracted from the literature (Tringale et al., 2018; Wu et al., 2018), the reimbursement schedule shown by the Centers for Medicare and Medicaid Services (CMS) (Centers for Medicare, 2023), or average wholesale price (AWP) (Pemetrexed, 2022; Tremelimumab, 2022; Durvalumab, 2023) and were then calculated by summing the drug's AWP plus costs of infusion

TABLE 1 Model parameters.

Parameter	Base-case value (range)	Distribution	Source
Cost			
Treatment cost ($/cycle)			
Durvalumab	1,380 (1,104–1,656)	Gamma	Durvalumab (2023)
Tremelimumab	9,360 (7,488–11,232)	Gamma	Tremelimumab (2022)
Abraxane	6,395 (5,116–7,674)	Gamma	Centers for Medicare (2023)
Pemetrexed	2,117 (1,693–2,540)	Gamma	Pemetrexed (2022)
Gemcitabine	78 (62–94)	Gamma	Centers for Medicare (2023)
Platinum doublet	12 (0.37–27)	Gamma	Centers for Medicare (2023)
Subsequent immunotherapy	12,592 (7,757–17,281)	Gamma	Centers for Medicare (2023)
Docetaxel	77 (62–92)	Gamma	Centers for Medicare (2023)
Radiotherapy	279 (223, 335)	Gamma	Centers for Medicare (2023)
Imaging	1,409 (1,127, 1,691)	Gamma	Criss et al. (2019)
BSC	637 (510–764)	Gamma	Criss et al. (2019)
Palliative care and death	15,957 (12,766, 19,148)	Gamma	Insinga et al. (2019)
Administration cost ($/cycle)			
Drug administration per hour	143 (114, 172)	Gamma	Criss et al. (2019)
Follow-up and monitoring	433 (346, 520)	Gamma	Insinga et al. (2019)
Cost to manageTRAEs ($/event)			
Anemia	5,243 (4,195, 6,292)	Gamma	Smith et al. (2002)
Neutropenia	16,857 (13,486, 20,229)	Gamma	Hornberger et al. (2015)
Thrombocytopenia	836 (669, 1,003)	Gamma	Insinga et al. (2019)
Neutrophil count decreased	907 (726, 1,088)	Gamma	Insinga et al. (2019)
Societal costs			
Patient time and salary loss ($/cycle)	550 (440, 660)	Gamma	Guérin et al. (2016)
Parking, meals, and travel ($/time)	33 (27, 40)	Gamma	Lauzier et al. (2011)
Caregiver ($/cycle)	640 (512, 768)	Gamma	Li et al. (2013)
Productivity loss ($/cycle)	881 (705, 1,057)	Gamma	Guérin et al. (2016)
Health utilities			
Disease status utility per year			
mNSCLC			
PFS	0.82 (0.65, 0.98)	Beta	Grutters et al. (2010)
PD	0.32 (0.26, 0.39)	Beta	Nafees et al. (2017)
Nonsquamous mNSCLC			
PFS	0.84 (0.67, 0.88)	Beta	Nafees et al. (2017)
PD	0.47 (0.17, 0.57)	Beta	Nafees et al. (2008)
Squamous mNSCLC			
PFS	0.71 (0.67, 0.76)	Beta	Chouaid et al. (2013)
PD	0.18 (0.14, 0.22)	Beta	Nafees et al. (2008)
TRAEs disutility per year			
Anemia	0.06 (0.05, 0.07)	Beta	Freeman et al. (2015)
Neutropenia	0.03 (0.02, 0.03)	Beta	Johnson et al. (2023)
Thrombocytopenia	0.11 (0.09, 0.13)	Beta	Tolley et al. (2013)
Neutrophil count decreased	0.03 (0.02, 0.03)	Beta	Hornberger et al. (2015)
Risk of TRAEs (%, rate of grade 3/4 over 5%)			
T+D+CT			
Anemia	17.27 (13.82, 20.73)	Beta	Johnson et al. (2023)
Neutropenia	16.06 (12.85, 19.27)	Beta	Johnson et al. (2023)

(Continued on following page)

TABLE 1 (*Continued*) Model parameters.

Parameter	Base-case value (range)	Distribution	Source
Thrombocytopenia	5.45 (4.36, 6.55)	Beta	Johnson et al. (2023)
Neutrophil count decreased	7.27 (5.82, 8.73)	Beta	Johnson et al. (2023)
D+CT			
Anemia	15.27 (12.22, 18.32)	Beta	Johnson et al. (2023)
Neutropenia	12.57 (10.06, 15.09)	Beta	Johnson et al. (2023)
Thrombocytopenia	4.49 (3.59, 5.39)	Beta	Johnson et al. (2023)
Neutrophil count decreased	7.19 (5.75, 8.62)	Beta	Johnson et al. (2023)
CT			
Anemia	2.04 (16.34, 24.50)	Beta	Johnson et al. (2023)
Neutropenia	12.01 (9.61, 14.41)	Beta	Johnson et al. (2023)
Thrombocytopenia	5.11 (4.08, 6.13)	Beta	Johnson et al. (2023)
Neutrophil count decreased	7.51 (6.01, 9.01)	Beta	Johnson et al. (2023)
Annual discount rate (%)	3 (1, 5)	Beta	Murray et al. (2000)

BSC, best supportive care; TRAEs, treatment-related adverse events; mNSCLC, metastatic non-small cell lung cancer; PFS, progression-free disease; PD, progressive disease; T+D+CT, tremelimumab plus durvalumab and chemotherapy; D+CT, durvalumab plus chemotherapy; CT, chemotherapy alone.

and follow-up and monitoring (Tringale et al., 2018; Wu et al., 2018). Costs to manage TRAEs were included as a weighted average based on the number of reported severe TRAEs (grades 3/4) in the clinical trial (Johnson et al., 2023). Costs of imaging, BSC, radiotherapy, and palliative care and death were obtained from the literature (Sher et al., 2011; Criss et al., 2019; Insinga et al., 2019). The model to depict the societal perspective incorporated informal healthcare costs (patient time and/or salary, transportation, and caregiver costs) (Lauzier et al., 2011; Li et al., 2013; Guérin et al., 2016) and non-healthcare costs (productivity loss) (Guérin et al., 2016).

2.3.3 Health utilities

Health utility was measured on a scale of 0–1, with 1 corresponding to optimal health and 0 corresponding to death; specific values in this study were obtained from published literature (Sanders et al., 2016). A decrement in health utility was known as disutility and occurred when experiencing TRAEs. Disutility associated with specific TRAEs were extended over a cycle period and their weighted averages were calculated paralleling their frequency in the POSEIDON clinical trial (Table 1). A weighted aggregate of health utilities overtime was used to measure QALYs, which reflected treatment effectiveness.

2.4 Statistical analysis

2.4.1 Cost-effectiveness analysis

The ICERs of T+D+CT vs. CT and T+D+CT vs. D+CT were used to assess the cost-effectiveness, which were measured using the incremental total healthcare or social costs divided by the incremental total QALYs. Treatment was considered cost-effective when the ICER was less than the WTP of $100,000/QALY (Neumann et al., 2014). The ICERs were rounded to the nearest $100,000. The impact inventory for the parameters considered in economic analyses was provided in Table 1.

2.4.2 Sensitivity analysis

One-way deterministic sensitivity analyses (OWSAs) and probabilistic sensitivity analyses (PSAs) were performed to assess the impact of parameter uncertainties on ICERs. In the sensitivity analysis, costs were modeled with gamma distributions, and health utilities, transition probabilities, and rates of TRAEs and discount were modeled with beta distributions. Standard deviations (SDs) for each distribution were obtained from the literature when possible. Unknown SDs were calculated using 20% of the mean. PSAs simulated 10,000 variations of all model parameters. In addition, we analyzed the expected value of perfect information (EVPI) to evaluate uncertainty in allocating treatment to the appropriate patients who might benefit in the most cost-effective manner.

2.4.3 Scenario analysis

Patients who still adhered to the treatments in the trial at the final data collection point (24 July 2019) were included in the scenario analysis. Assuming these patients had been cured, they discontinued the aforementioned therapies but were still followed up monthly until 15 years. The survival data followed the age-adjusted survival probabilities of the general US population provided by actuarial life tables from the US Social Security Administration (Courtney et al., 2021).

2.4.4 Subgroup analysis

In POSEIDON, patients with squamous histology receiving T+D+CT benefited less in PFS and OS than those with non-squamous histology, even if they experienced improved benefits compared with the CheckMate 227 trial (another clinical trial that observed CTLA-4 plus PD-L1 and chemotherapy for mNSCLC) (Hellmann et al., 2019; Johnson et al., 2023). Therefore, subgroup analysis was conducted to explore possible heterogeneity between patients with non-squamous mNSCLC and squamous mNSCLC.

3 Results

3.1 Base case analysis

From the perspective of the US healthcare, T+D+CT was associated with an increased cost of $7,108 from $360,968 for CT and an increased cost of $27,779 from $340,297 for D+CT. Treatment with T+D+CT yielded a gain of 0.09 QALYs from 0.46 QALYs for CT and a gain of 0.02 QALYs from 0.53 QALYs for D+CT, resulting in ICERs of $82,501/QALY for CT and $1,243,868/QALY for D+CT. From the societal perspective, T+D+CT vs. CT was associated with an additional cost of $445, which gained an ICER of $5,167/QALY, and the T+D+CT vs. D+CT yielded cost savings of $2. At the WTP of $100,000, T+D+CT was considered cost-effective compared with CT but was not cost-effective compared with D+CT from the perspective of the healthcare sector. It was considered highly cost-effective compared with CT or D+CT from the societal perspective (Supplementary eTable S2).

Results of scenario analysis were consistent with the base case analysis (Supplementary eTable S2). Results of the short-term cost-effectiveness analysis did not support that T+D+CT was an economical treatment compared with CT from the perspective of the healthcare sector (Supplementary eTable S3). The subgroup analysis found that T+D+CT vs. CT or D+CT entailed lower incremental costs and higher incremental QALYs among patients with non-squamous mNSCLC than patients with squamous mNSCLC. The T+D+CT vs. CT remained cost-effective among patients with non-squamous mNSCLC from the perspective of the healthcare sector whilst being not cost-effective among patients with squamous mNSCLC (Supplementary eTable S4).

3.2 One-way sensitivity analyses

From the perspective of the US healthcare sector, the annual discount rate was the primary factor affecting ICER (Supplementary eFigure S2). For T+D+CT vs. CT, the model was also sensitive to the costs of subsequent immunotherapy, tremelimumab, palliative care and death, pemetrexed cost, and durvalumab, which altogether affected the cost-effectiveness of T+D+CT (Supplementary eFigure S2). If T+D+CT was cost-effective compared with CT, the annual discount rate should be controlled under 3.12%. Alternatively, treatment costs should be controlled under $9,746 for tremelimumab, under $3,970 for pemetrexed, or under $1,534 for durvalumab. When the cost subsequent immunotherapy was contained within $11,729 or that the cost of palliative care and death was contained within $15,072, the CT would become an economical option. Although the cost of tremelimumab, cost of palliative care, cost of death, PD utility, and PFS utility were the top five factors affecting the economics of T+D+CT vs. D+CT, none of them could make ICER lower than the WTP threshold of $100,000 (Supplementary eFigure S2). In addition, the cost-effectiveness of T+D+CT was associated with the period of receiving durvalumab monotherapy post-PD and it was considered cost-effective compared with CT if the period was more than 10 months. The T+D+CT had the lowest ICER compared with D+CT after receiving a four-month durvalumab monotherapy during PD, which was still over $100,000. From the societal perspective, all parameters were unlikely to change the cost-effectiveness of T+D+CT vs. CT or D+CT. The T+D+CT was always an economical option from the societal perspective, unbothered by any parameters.

3.3 Probabilistic sensitivity analysis

From the perspective of the healthcare sector, the probability of T+D+CT being cost-effective compared with CT was 59% at a threshold of $100,000/QALY and 82% at a threshold of $150,000/QALY (Figure 2), while it was only 0.04% compared with D+CT even if the WTP increased to $700,000/QALY (Supplementary eFigure S3). From the societal perspective, the probability of T+D+CT being cost-effective was 100% at the threshold of $100,000/QALY (Supplementary eFigure S3).

By changing the horizon of simulation time, it was found that the minimum value of ICERs for T+D+CT vs. CT and T+D+CT vs. D+CT were 13 years (Supplementary eFigure S4). Therefore, we calculated the EVPI of T+D+CT vs. CT or D+CT for a 13-year simulation time horizon. The EVPIs were estimated to be $1811.53 per patient for T+D+CT vs. CT, and $0.00 per patient for T+D+CT vs. D+CT.

4 Discussion

In this cost-effectiveness analysis, we found that T+D+CT could be considered cost-effective, compared with CT, as the first-line treatment for patients with mNSCLC, though this was not the case when T+D+CT was compared with D+CT. Our model for T+D+CT vs. CT was particularly sensitive to assumptions regarding the annual discount rate and treatment costs. The model for T+D+CT vs. D+CT was also sensitive to health utilities, but these assumptions did not change the cost-effectiveness of T+D+CT vs. D+CT. To our knowledge, this is the first study to evaluate the cost-effectiveness of fist-line T+D+CT for mNSCLC from the perspectives of the US healthcare sector and the society.

Pemetrexed and durvalumab were the main treatment options for the T+D+CT and D+CT arms during the maintenance phase, the costs of which were factors that, in this study, only the model of T+D+CT vs. CT was sensitive to. The shorter duration of pemetrexed and durvalumab in the short-term cost-effectiveness analysis did not show the economics of T+D+CT compared with CT, indicating that the duration of immunotherapy is also a factor affecting the economics of the treatment, but there is currently no clear definition of the duration of immunotherapy (Courtney et al., 2021). Both the models of T+D+CT vs. CT and T+D+CT vs. D+CT showed sensitivity to the cost of tremelimumab, which was only used in the T+D+CT arm. The proportions of patients with PD or death and patients receiving subsequent immunotherapy after PD in the CT arm were significantly higher than that in the T+D+CT and D+CT arms. Controlling the costs of subsequent immunotherapy and palliative care and death would help to reduce the treatment costs of the CT arm.

The sensitivity analysis showed that T+D+CT in patients who continued to receive durvalumab for 10 months or more after PD was cost-effective compared with CT. The phase-III ARCTIC

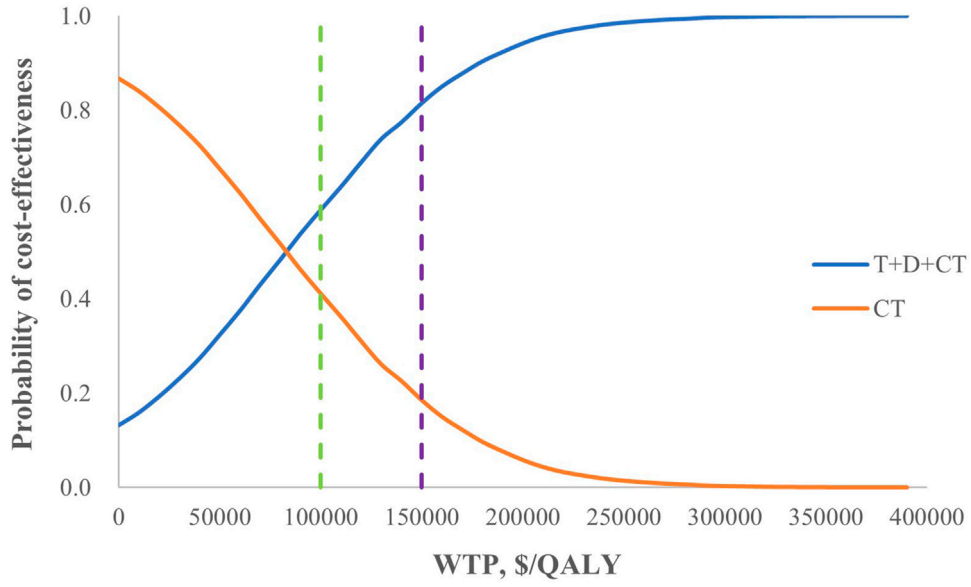

FIGURE 2
Cost-effectiveness acceptability curves for T+D+CT vs. CT from the perspective of the healthcare sector. T+D+CT, tremelimumab plus durvalumab and chemotherapy; CT, chemotherapy alone.

(NCT02352948) trial reported that the median duration of response (DoR) among patients receiving T+D as the third-line treatment was 12.2 months, which was longer than that of the POSEIDON trial (9.5 months) and included the ten-month duration (Planchard et al., 2020). The subgroup analysis proved that histology was among factors affecting the economics of T+D+CT compared with CT and the median DoR of patients with non-squamous mNSCLC was significantly longer than that of patients with squamous mNSCLC in the T+D+CT arm (16.4 months vs. 5.6 months) (Johnson et al., 2023). The difference in the proportion of patients with non-squamous mNSCLC (63.31% in the POSEIDON trial vs. 75.86% in the ARCTIC trial) and the expression of PD-L1 (only patients with a tumor proportion score of 25% or more received T+D in the ARCTIC trial, patients with tumor proportion score less than 25% also received T+D+CT in the POSEIDON trial) may be partly responsible for the difference in the median DoR between POSEIDON and ARCTIC trials (Planchard et al., 2020; Johnson et al., 2023). At the WTP threshold of $100,000/QALY, patients could continue to receive durvalumab for 10 months or more after PD if they meet the criteria, which could be extended for patients scoring over 25% on tumor proportion or patients with non-squamous mNSCLC.

We explored the impact of uncertainties on decision-making by conducting probabilistic sensitivity analyses over 10,000 simulations. Based on our EVPI outcomes, when all uncertainties were considered and the best treatment option was identified for each individual patient, patients with mNSCLC in the US were projected to save a total of $601 million when eligible patients received T+D+CT, $53 million when eligible patients received D+CT, and $832 million when eligible patients received CT (Siegel et al., 2021).

Two earlier phase-III trials (MYSTIC and NEPTUNE) of T+D vs. CT as the first-line treatment for mNSCLC did not show any statistically significant improvement in OS between T+D and CT (Rizvi et al., 2020; de Castro et al., 2023). The MYSTIC trial (NCT02453282), conducted among mNSCLC patients with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, did not meet its primary end points of improved OS or PFS for T+D vs. CT in patients with over 25% tumor proportion score, but identified a tumor mutational burden from blood (bTMB) threshold of 20 mut/Mb for optimal OS benefit (Rizvi et al., 2020). The POSEIDON trial considered the bTMB ≥ 20 mut/Mb population when tested the secondary endpoint of OS for T+D+CT vs. CT after meeting the primary endpoints of OS and PFS benefits (Johnson et al., 2023). However, the NEPTUNE trial (NCT02453282) for mNSCLC with EGFR and ALK mutations missed its primary end point of improved OS for T+D vs. CT in patients with bTMB≥20 mut/Mb (de Castro et al., 2023).

Except for mNSCLC, durvalumab in combination with tremelimumab has been approved for patients with unresectable hepatocellular carcinoma (uHCC) in the US based on the HIMALAYA trial (NCT03298451) (Abou-Alfa et al., 2022). The indications of mNSCLC and uHCC were under regulatory review in several regions and countries worldwide, including Europe, Japan, Australia, Canada, and China (Keam, 2023). In addition, the evaluation for some other indications is also ongoing, though little supporting evidence has been generated. In this regard, the CASPIAN trial (NCT03043872) for extensive-stage small cell lung cancer showed that adding T+D to platinum-etoposide was not more effective than platinum-etoposide alone as the first-line treatment (Goldman et al., 2021). The DANUBE trial (NCT02516241) for unresectable, locally advanced or metastatic urothelial carcinoma showed that T+D was not more effective than CT as the first-line treatment (Powles et al., 2020). The phase-II trials for advanced biliary tract cancer, progressive, refractory,

advanced thyroid carcinoma, cervical cancer, and tumor mutational burden-high and/or microsatellite instability-high of advanced solid tumors are also ongoing (Keam, 2023).

The positive clinical outcomes and cost-effectiveness data from our study can support providers in advocating for the inclusion of this combination therapy in treatment protocols. Providers can balance clinical efficacy with financial considerations to guide patients towards therapies that offer the best value. By presenting evidence of both the clinical benefits and the cost savings associated with this treatment, providers can make a stronger case for its adoption in clinical practice, potentially improving patient outcomes and reducing overall healthcare costs. For policy stakeholders, our findings offer valuable evidence to support policy discussions about including cost-effective treatments in formularies. Although cost-effectiveness is not typically the primary criterion for formulary decisions in the US, the growing emphasis on value-based care models could lead to greater consideration of economic evaluations. Our study can inform budget impact analyses, helping policymakers understand the long-term economic benefits of adopting durvalumab plus tremelimumab. Additionally, this evidence can influence reimbursement policies by highlighting the potential for cost savings and improved patient outcomes, encouraging the adoption of more cost-effective therapies through value-based reimbursement schemes. Future research should focus on gathering real-world evidence to validate the cost-effectiveness of this combination therapy in diverse patient populations. This can help address any discrepancies between clinical trial populations and routine care settings. Additionally, studies that specifically analyze the impact of cost-effectiveness evidence on formulary decisions and healthcare policies in the US can provide insights into how such evidence can be more effectively utilized in the decision-making process. By continuing to build on this foundation, researchers can contribute to a more comprehensive understanding of the value of new treatments in real-world settings, ultimately guiding better healthcare decisions and policy formulations.

5 Limitations

Our analysis has several limitations. First, the survival data and treatment strategies used in our model were only from one phase III randomized controlled trial (POSEIDON). The trial population may be slightly younger and healthier compared to the general population, potentially leading to differences in treatment tolerance and outcomes. Differences in income level and insurance type can affect access to treatment and adherence, potentially influencing real-world effectiveness. While efforts were made to include a diverse population, certain racial and ethnic groups might still be underrepresented, which could affect the generalizability of the findings. The results of more clinical studies could help to build a more robust prediction model. However, the other two published phase-III clinical studies did not meet the primary endpoint of OS (or PFS) benefits. Second, the health utilities and treatment costs used in this study were mainly derived from previous studies, whose research protocol and patient characteristics differed from those of the POSEIDON trial. Although the cost-effectiveness analysis from the perspective of the US healthcare sector showed that T+D+CT was cost-effective compared with CT and was not cost-effective compared with D+CT, the results of clinical trials conducted in individual patients or by other medical institutions may be different, as models were sensitive to assumptions of health utilities and treatment costs in the sensitivity analysis. Third, many alternative treatment options for mNSCLC were not assumed. However, the results may not be overturned by these unassumed parts as the proportion of patients who chose other treatments during the subsequent anticancer therapy in the POSEIDON trial was small and the ICERs of T+D+CT relative to CT and D+CT were far from the threshold of WTP. Fourth, this study did not take into account the impact of some factors related to the effectiveness on the economics of the treatment. The POSEIDON trial only considered two PD-L1 expression levels, 50% and 1%. If 25% was used as the cutoff, whether it would produce different economic results is unknown. In addition, the trial did not report the survival data of patients with bTMB $\geq$ 20 and bTMB $<$ 20, whether the economic results were related to the bTMB level is also unknown.

6 Conclusion

This economic evaluation found that D+T+CT could be considered cost-effective if compared with CT alone but could not if compared with D+CT as the first-line treatment for patients with mNSCLC from the perspective of the US healthcare sector. However, these results only stood true in the non-squamous mNSCLC cohorts. The results of squamous mNSCLC cohorts did not support the economics of D+T+CT compared with CT alone. From the societal perspective, D+T+CT was cost-effective, independent of histology. Alongside improving patient survival, the duration and high-cost of immunotherapy are also issues to be considered by the healthcare sector (Durvalumab, 2023).

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

YG: Writing–original draft, Writing–review and editing. FS: Writing–review and editing. HZ: Writing–review and editing. HL: Writing–review and editing. SH: Writing–review and editing. DL: Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1256992/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 June 2024
DOI 10.3389/fphar.2024.1298923

OPEN ACCESS

EDITED BY
Michael Ekubu Otim,
Dubai Medical University, United Arab Emirates

REVIEWED BY
Segundo Mariz,
European Medicines Agency, Netherlands
Keith Tolley,
Independent Researcher, Buxton, Derbyshire, United Kingdom

*CORRESPONDENCE
Aniek Dane,
a.dane@erasmusmc.nl

RECEIVED 22 September 2023
ACCEPTED 29 May 2024
PUBLISHED 24 June 2024

CITATION
Dane A, Uyl-de Groot C and van der Kuy H (2024), Unraveling elements of value-based pricing from a pharmaceutical industry's perspective: a scoping review.
Front. Pharmacol. 15:1298923.
doi: 10.3389/fphar.2024.1298923

Unraveling elements of value-based pricing from a pharmaceutical industry's perspective: a scoping review

Aniek Dane[1]*, Carin Uyl-de Groot[2] and Hugo van der Kuy[1]

[1]Department of Hospital Pharmacy, Erasmus MC, Rotterdam, Netherlands, [2]Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, Netherlands

Health authorities use value-based pricing models to determine the value of innovative drugs and to establish a price. Pharmaceutical companies prefer value-based pricing over cost-based pricing. It is ambiguous whether value-based pricing has the same meaning to these stakeholders. We aimed to identify the elements that attribute to value-based pricing of innovative drugs from a pharmaceutical industry's perspective and as possible starting point for (value-based) contracting of drugs. We performed a scoping review of publications available in scientific databases with terms such as 'value-based pricing', 'pharmacoeconomics', 'drug cost', 'innovative drug' and 'drug therapy'. We included 31 publications, covering value elements of innovative drugs from a pharmaceutical industry's perspective. Overall, all found elements of value-based pricing were congruent with the elements of value-based pricing from a health authority's perspective. However, the emphasis placed on the elements differed. The most frequently mentioned elements in our review were economic considerations and cost aspects. Least mentioned were elements regarding cost-effectiveness, disease characteristics and patient characteristics. Although all elements in the drug value framework were present which indicate congruity, there seems controversy on the importance of cost-effectiveness as an element of value. Consequently, establishing a coherent and to all stakeholders' acceptable framework to value and price innovative drugs seems complicated. Mutual understanding can be found in the value elements societal considerations and healthcare process benefits. Our results supported the importance of economic and cost aspects regarding determination of prices of innovative drugs. Further research is required to quantify the weights of all relevant elements in the drug value framework, observe their possible interlinkages, and to weigh them over time.

KEYWORDS

drug pricing, health economics, health policy, innovative drugs, pharmaceutical industry, pharmacoeconomics, value-based pricing (VBP)

1 Introduction

As costs of pharmaceuticals keep rising, policymakers, legislators, healthcare professionals, health insurance companies and patients expect pharmaceutical companies to clarify their pricing regimes. However, pharmaceutical companies seem reluctant to disclose their pricing strategies and their ways of determining launch prices of drugs brought to market (Simoens, 2011; Wahlster et al., 2014; Vogler et al., 2017; UCL

Institute for Innovation and Public Purpose, 2018; European Commission, 2020; Neumann et al., 2021). This need for transparency is increasing as a growing burden is placed on healthcare systems to ensure sustainable access to healthcare for all patients while budgets are limited (Simoens, 2011; Vogler and Paterson, 2017). Moreover, these prices serve as starting points for price negotiations, contracting and reimbursement decisions later in the process. This is particularly the case for innovative drugs, defined as a completely or partially new active substance or biological entity, or (a) combination of such entities, acting against a disease, relieving symptoms, or preventing a disease through pharmacological or molecular mechanisms, and developed and made available as a medicinal product that can improve the quality of patient management and outcomes (Erice Group, 2008).

In the cases of Kalydeco® and Orkambi®, drugs for the treatment of cystic fibrosis, health insurance systems are faced with significant reimbursement challenges upon market entry (Hollis, 2019). The same goes for the reimbursement of Zolgensma®, a gene therapy for spinal muscular atrophy, which was heavily debated in the Netherlands (National Health Care Institute, 2021). This drug, which is considered the most expensive drug up to date (Nuijten, 2022), is priced $2.1 million per (one-time) treatment.

Generally, pharmaceutical companies state that prices cannot be calculated by means of a simple equation of several cost aspects, multiplied by a profit margin, the so-called cost-based pricing method (Gregson et al., 2005b). Particularly research & development (R&D) costs seem difficult to attribute to a specific drug, and cost of failures in R&D–promising medicines that eventually do not reach the market–have to be discounted in prices of drugs that do reach the market (DiMasi, 2018). Because of this complexity, pharmaceutical companies prefer to focus on the value of a drug instead of its costs (Gregson et al., 2005b; UCL Institute for Innovation and Public Purpose, 2018). The question arises what value is and how to translate this to pricing methods.

Since 2013, starting with the taxonomy of value-based pricing of drugs by Sussex et al. upon request of the British government, policymakers have assumed that the price of a drug can be considered a function of the perception of its value to patients and society (Towse and Barnsley, 2013a; Sussex et al., 2013). Moreover, the World Health Organization's (WHO) Collaborating Centre for Pharmaceutical Pricing and Reimbursement Information has defined value-based pricing as 'setting a price of a new medicine and/or decide on reimbursement based on the therapeutic value a medicine offers, usually assessed through several health technology assessments (HTA) or economic evaluations, which differ by country (WHO Collaborating centre Pharmaceutical Pricing and Reimbursement Information, 2016; Tafuri et al., 2022). However, the value of innovative drugs is a largely unmeasured and misunderstood term (Petrou, 2017). As Petrou described, a definition of real value which is accentuated by superior and significant results in hard and clinically meaningful endpoints is rare in the pharmaceutical sector (Petrou, 2017). Reimbursement agencies determine the value of innovative drugs based on pharma-economic evaluations such as HTA, but these calculations hardly correspond with the prices proposed by the pharmaceutical industry. Therefore, nowadays, it is seen in the United States that payers and pharmaceutical manufacturers have agreed on value-based purchasing contracts in order to link patient outcome to price, amount or nature of reimbursement (Kannarkat et al., 2020; Swart et al., 2020). Nonetheless, Wise et al. stated that the biopharma's challenge is that the term 'value' might mean different things to different stakeholders: 'value' perceived as important by the regulatory agency as a therapeutic for a disease in a child might not be the value that is being sought by the patient's parent or caregiver. Furthermore, outcomes and endpoints are defined differently by different stakeholders for different clinical scenarios (Wise et al., 2018). A richer evidence base and a more open dialog are needed if society is to become more patient-centered in its authorization of innovative therapies (Wise et al., 2018).

Moreover, although intertwined, value and innovation should not be considered alike, where innovation is just one of the determinants of value (Erice Group, 2008). Innovation could, furthermore, be related to other elements of value, such as contribution to scientific knowledge, public health and patient needs, social and economic needs, and environmental impact. Innovation, however, should be considered to be more general than value and comprehensive and invariant across setting and contexts. (Erice Group, 2008).

Based on their systematic review on pricing of medicines, Van der Gronde et al. concluded that value-based pricing and outcome-based pricing are the most promising long-term developments (Van der Gronde et al., 2017). Moreover, value-based pricing has emerged as a preferred alternative to prices determined to what the market will bear (Kaltenboeck, 2020) or other alternatives such as price referencing (Drummond et al., 1997). Nevertheless, it was argued that value-based pricing is more of an art than science due to lack of standardization of value-based pricing practice (Brooks and Geyer, 2016; Jommi et al., 2020) or deemed not appropriate for innovative drugs such as orphan drugs or gene and cell therapies (Drummond and Towse, 2019).

According to the methodological framework of Gregson et al., the value of a drug V is represented by the reference price R (standard of care) plus or minus the differential value D. However, it is not exactly clear what constitutes D in this equation, except that it is a mixture of clinical, economical, and quality of life improvements (Gregson et al., 2005). Furthermore, several methods exist to assess the value of drugs for decision making, although they differ in mission, scope of activities and methodological approaches (Vogler et al., 2017; Neumann et al., 2018). Specifically for oncology drugs, Uyl-de Groot & Löwenberg developed a pricing model based on cost-based-plus pricing to alter the balance between social and economic entrepreneurship. Their model entails elements such as cost of the drug, R&D costs in relation to number of patients, patent period left and profit margin (Uyl-De Groot and Löwenberg, 2018).

As mentioned, Sussex et al. developed a taxonomy of value-based pricing (Sussex et al., 2013), succeeded by drug value frameworks developed by Towse & Barnsley in 2013 (Towse and Barnsley, 2013b) and Paulden et al., in 2015 (Paulden et al., 2015). Furthermore, in 2016, PhRMA (Pharmaceutical Research and Manufacturers of America) has declared 15 principles for value assessment frameworks (PhRMA, 2016). This declaration was primarily a response to the value frameworks that were developed to accommodate policy making and pricing decisions of reimbursement agencies and governments. In 2020, the EFPIA

(European Federation of Pharmaceutical Industries and Associates) has presented novel pricing and payment models to improve patient access to innovative drugs (EFPIA, 2020). Five principles were set to shape and guide discussions on these pricing models, whereas one of them was the value principle; a high quality, methodologically and mutually agreed value-based framework. However, neither the PhRMA principles nor the EFPIA value principles clearly reveal which elements should be used to determine the value of innovative drugs within the context of value-based pricing. Hence, systematic data that contribute to transparency of pharmaceutical drug pricing and the way value is determined, remain scarce and incomplete (Prasad et al., 2017) and is mainly focused on revealing costs of R&D (DiMasi et al., 2016). Furthermore, in the case of orphan drugs and new cell and gene therapies the need for new approaches to existing drug value frameworks increases (Coyle et al., 2020; Tafuri et al., 2022). Up to date hardly any coherent data or studies exist regarding the value-based pricing methodology of innovative drugs that is used by the pharmaceutical industry. Meanwhile, in March 2017, the European Parliament has adopted a resolution on European Union options for improving access to medicines, which calls for full transparency on the procedures used to determine prices of medical products (European Parliament, 2017).

In an attempt to resolve the controversy over transparency, we believed that governmental policymakers, reimbursement agencies and pharmaceutical companies together should cooperate and decide on the use of jointly accepted drug value framework. This may be useful when, after entering a country's market, governmental, health authorities, health insurers and care providers –- depending on the country - start various kinds of HTA and/or cost-effectiveness assessments, managed entry agreements and price negotiations, and reimbursement arrangements as part of the (value-based) contracting process.

From literature, we were acquainted with drug value frameworks from a policymaker's perspective, but we were unaware what resembled a drug value framework from a pharmaceutical perspective. Therefore, the aim of our study was to identify the pricing elements that attribute to the value of innovative drugs as perceived by the pharmaceutical industry. A scoping review was chosen in order to identify and map key characteristics to the concept of value-based pricing (Munn et al., 2018).

2 Methods

2.1 Search strategy

We performed a systematic search strategy to collect and analyze elements of value-based pricing. We limited our search to publications in scientific journals to avoid public debates and marketing statements on the subject published in grey literature.

The review was performed in five subsequent steps: 1) identification of publications; 2) screening titles and abstracts; 3) screening full texts; 4) analyzing full texts by means of a value framework, and 5) validation.

First, published studies were identified using the electronic databases Embase, Medline, Web of Science, Econlit and Google Scholar. Searches were performed with terms such as 'pricing', 'pharmacoeconomics', 'drug cost', 'orphan drug', 'drug therapy', 'value-based pricing', 'pharmaceutical', 'innovation', 'rare disease' and 'medicine'. The complete search strategy is presented in File S1 in the Supplementary Material. The initial search was performed in February 2020 and updated in August 2022 and included all publications from inception to date that matched with the targeted word combinations. No additional filters for language or quality of evidence were applied at this stage. Only duplicate records were excluded from the initial abstract screening.

To execute the second step–screening titles and abstracts–a list of criteria was made to include eligible publications. Publications were included if they met the following criteria: 1) pharmaceutical industry's perspective; 2) situated in high-income and OECD (Organization for Economic Cooperation and Development) country; 3) mentioning drug pricing, drugs costs and/or value of drugs; 4) describing price elements and/or value elements; 5) studying pricing of innovative prescription drugs and/or orphan drugs.

We choose these particular criteria for the following reasons. Criterion one was selected to only include articles which were written from a pharmaceutical industry's point of view, since the aim of this study was to identify elements of value-based pricing from this perspective. Criterion two was selected because pricing or value discussions on pharmaceuticals differ between high- and low-income countries (OECD, 2008). Criteria three and four were selected to include articles on pricing and value and to explicitly exclude articles on economic, cost or cost-effectiveness analyses of specific drugs for not being the area of research in this study. Furthermore, we did not distinguish between prices or value of drugs at launch or at a later point in time–e.g., we included both patented drugs and drugs after patent expiry. Finally, criterion five was selected to include articles discussing innovative pharmaceuticals and to exclude pricing of generic pharmaceuticals or over-the-counter (OTC) drugs. Furthermore, Abstracts (A) and summaries (S) were excluded.

The third step consisted of screening full texts. Eligible publications had to be written in English and had to be available for reviewing. Publications were excluded if they did not meet these criteria. In order to analyze the full texts of the included publications in the fourth step, a framework was generated based on elements that all were present in the existing drug value frameworks of Sussex et al., Towse & Barnsley, Paulden et al. and Lakdawalla et al. (Towse and Barnsley, 2013a; Sussex et al., 2013; Paulden et al., 2015; Lakdawalla et al., 2018). From these models we extracted the following elements: health effects (e.g., quality of live, (cost-) effectiveness, outcomes); patient and disease characteristics (e.g., child/adult, unmet need, severity and rarity); societal benefits (e.g., increased labor productivity, health gain on population level); healthcare process related aspects (e.g., convenience in administration, less time-consuming, reduced hospitalizations); innovation (advancement of scientific knowledge achieved by the development of medicines (Sussex and Towse, 2013), future products as a consequence of approval of a product today (Towse and Barnsley, 2013b), scientific spillover; future benefits of current innovations (Lakdawalla et al., 2018)); risks (e.g., uncertainty of outcome, financial risks, legal considerations); costs (e.g., cost of R&D, cost of capital, cost of failure) and economic factors (e.g., business, industrial and commercial considerations).

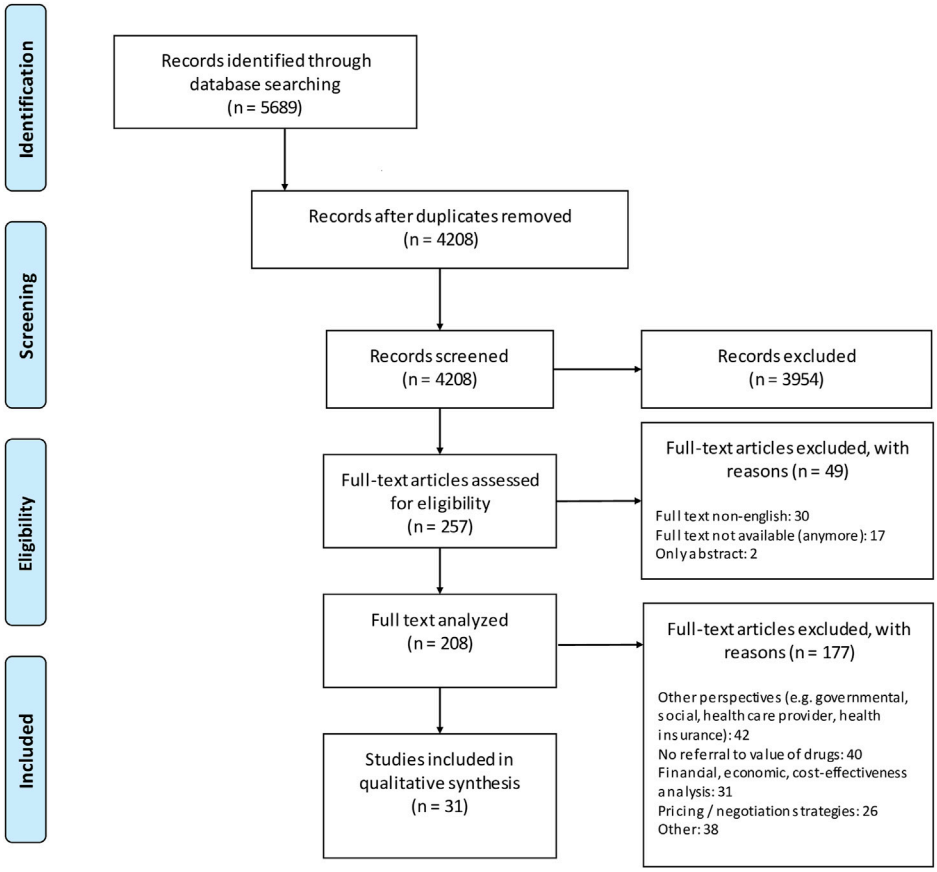

FIGURE 1
Flow chart.

For structuring and quality and sensitivity analysis of the included articles additional data were collected: first author; year of publication; publication source; type of publication; studied country/countries; research period; objective; medical condition; described name of the drug; composition of the drug; type of drug; involvement of pharmaceutical industry with the publication. While analyzing, relevant text passages of the included publications were copied and pasted into the framework and highlighted for quick recognition. The last step was initiated to minimize the risk of selection bias and to enhance internal validity and consisted of analyzing a random sample of included publications after completion of the framework by the two authors not involved in analyzing full texts of all included publications.

2.2 Quality assessment

Overall, to minimize the risk of bias several co-workers were involved. To conduct the literature search and extraction of the eligible publications one of the authors, (AD), was supported by a co-worker of the Erasmus MC Medical Library. Subsequently, all authors, independently, screened the titles and abstracts, thereby looking for publications that met the above-mentioned criteria. Next, one author (AD) screened the full texts of the publications included and then analyzed these publications using the developed framework. Successively, one co-worker of the Erasmus MC Hospital Pharmacy Department independently analyzed the full texts of the included publications. The two separately filed out frameworks were then compared and discussed. Lastly, two authors (CU, HK) each analyzed a random sample of six of the eligible publications of the third round and compared their findings with the completed framework. Differences were resolved via discussion and consensus. To ensure the quality of reporting, the Preferred Reporting Items for the Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist was used (Tricco et al., 2018). The completed checklist is available in File S2 of the Supplementary Material. Furthermore, a sensitivity analysis was performed by withdrawing low quality publications such as case reports and conference papers. We did not register or publicly publish the study protocol.

3 Results

3.1 Literature search results

The database search identified 5,689 unique publications. The final number of publications included in the review was 31. The flow

TABLE 1 Overview of included publications and results*.

General information	Publication year	Studied countries	Publication type	Drug type	Involvement of pharmaceutical industry
	1990–2000: 5 Siegelman S (1991) Vagelos PR (1991) Weidenbaum ML (1993) Murray MD (1998) Lu ZJ (1998) **2001–2010: 8** Calfee JE (2001) Dockhorn RJ (2005) Ruffolo RR (2005) Sollano J (2008) Tambuyzer E (2010) Lockhart MM (2010) Reinhart R (2010) Zhong X (2010) **2011–2022: 18** Davies JE (2012) Numerof RE (2012) Dickov V (2012) Rollet P (2013) Silverman E (2013) Saadi E (2014) Winegarden W (2014) Kibble A (2015) Gutierrez L (2015) Morrison C (2015) Pauwels K (2016) Patel KR (2017) Wise J (2018) Barkan J (2019) de Sola-Morales O (2019) Coyle D (2020) Garrison LP (2021) Postma MJ (2022)	**USA: 14** Siegelman S; Vagelos PR; Weidenbaum ML; Murray MD; Lu ZJ Calfee JE Dockhorn RJ; Ruffolo RR Sollano J; Silverman E; Winegarden W; Patel KR; Garrison LP **Developed/high income countries: 10** Zhong X; Davies JE; Numerof RE; Dickov V; Saadi E; Morrison C; Wise J; Barkan J; Coyle D; Postma MJ **Europe: 4** Rollet P, Kibble A, Guttierrez L, de Sola-Morales O **US/Europe/Japan: 1** Tambuyzer E **Belgium: 1** Pauwels K **New Sealand:** Lockhart R	**Journal article - review: 14** Vagelos PR; Weidenbaum ML; Murray MD; Dockhorn RJ; Sollano J; Reinhart R; Zhong X; Davies JE Dickov V; Rollet P; Patel KR; Wise J; Coyle D; Postma MJ **Journal article - opinion: 6** Calfee JE; Tambuyzer E; Silverman E; Saadi E; Gutierrez L; Garrison LP **Conference summary: 2** Kibble A, Barkan J **Journal article - qualitative analysis: 2** Lockhart MM, Pauwels K **Journal article - quantitative analysis: 1** Lu ZJ **Journal article - special report: 1** Siegelman S **Journal article - editorial: 1**de Sola-Morales O **Journal article - news: 1** Morrison C **Magazine article - opinion**: 1 Numerof RE **Report**: 1 Winegarden W **Case report**: 1 Ruffolo RR	**Prescription drugs: 13** Siegelman E; Vagelos PR; Weidenbaum ML; Murray MD; Calfee JE; Ruffolo RR; Sollano J; Lockhart MM; Zhong X; Davies JE; Numerof RE; Kibble A; Wise J **Orphan drugs: 10** Dockhorn RJ; Tambuyzer E; Reinhart R; Rollet P; Silverman E; Gutierrez L; Morison C; Patel KR, de Sola-Morales O; Postma MJ **Patented/innovative drugs: 8** Lu ZJ; Dickov V; Saadi E; Winegarden W; Pauwels K; Barkan J; Coyle D; Garrison LP	**Yes: 21** Vagelos PR; Lu ZJ; Calfee JE; Dockhorn J; Ruffolo RR; Sollano J; Tambuyzer E; Reinhart R; Zhong X; Davies JE; Numerof RE; Rollet P; Silverman E; Saadi E; Gutierrez L; Pauwels K; Wise J; de Sola-Morales O; Coyle D; Garrison LP; Postma MJ **No/unknown: 10**> Siegelman S; Weidenbaum ML; Murray MD; Lockhart MM; Dickov V; Winegarden W; Kibble A; Morison C; Patel KR; Barkan J
Societal considerations: 30	**Social/unmet needs: 7**	**Quality of life on a population level: 7**	**Increased productivity: 6**	**Impact on healthcare budget: 8**	**Insurance value: 2**
	Vagelos PR; Wise J; de Sola-Morales O; Morrison C; Weidenbaum ML; Saadi E; Gutierrez L	Siegelman S; Vagelos PR; Saadi E; Wise J; Davies JE; Coyle D; Garrison LP	Siegelman S; Vagelos PR; Saadi E; Pauwels K; Wise J; Garrison LP	Pauwels K; de Sola-Morales O; Tambuyzer E; Rollet P; Weidenbaum ML; Coyle D (2**); Garrison LP	Coyle D; Postma MJ
Economic considerations: 42	**Return on investment: 18**	**Willingness-to-pay: 13**	**Country-specific pricing characteristics: 5**	**Competition: 6**	
	Vagelos PR; Weidenbaum ML; Calfee JE (3); Tambuyzer E (2); Lockhart MM; Zhong X; Rollet P; Numerof RE; Dickov V (2); Winegarden W (2); Murray MD; Pauwels K; Dockhorn RJ	Wise J; Calfee JE; Sollano J; Pauwels K; Morrison C; Tambuyzer E; Zhong X; Numerof RE; Silverman E; Dickov V; Saadi E; de Sola-Morales O; Coyle D	Vagelos PR; Wise J (2); Zhong X; de Sola-Morales O	Calfee JE; Lu ZJ; Vagelos PR; Rollet P; Pauwels K; Sollano J	
Healthcare process considerations: 31	**Superior treatment: 14**	**Reduction other costs of healthcare delivery: 10**	**Patient access: 3**	**Preferences: 2**	**Logistics & treatment challenges: 2**
	Vagelos PR (2); Weidenbaum ML; Zhong X; Numerof RE; Dickov V; Silverman E (2); Winegarden W; Gutierrez L; Morrison C Coyle D; Postma MJ; Garrison LP	Siegelman S; Pauwels K; Vagelos PR; Murray MD; Saadi E; Winegarden W; Morrison C; Wise J; Zhong X; Barkan J	Saadi E; Vagelos PR; Gutierrez L	Zhong X (2)	Coyle D; Postma MJ

(Continued on following page)

TABLE 1 (*Continued*) Overview of included publications and results*.

General information	Publication year	Studied countries	Publication type	Drug type	Involvement of pharmaceutical industry
Patient characteristics: 9	**Heterogeneity of patients: 3**	**Knowledge of patient population: 3**	**Personalized medicine: 2**	**Patient's weight: 1**	
	Zhong X; Gutierrez L; Rollet P	Numerof RE; Gutierrez L; Barkan J	Zhong X; Numerof RE	Morrison C	
Disease characteristics: 14	**Disease rarity: 6**	**Type of disease: 3**	**Disease heterogeneity: 3**	**Other treatment options: 1**	**Disease severity: 1**
	Tambuyzer E; Silverman E; Gutierrez L; Rollet P; Barkan J; Davies JE	Lu ZJ; Saadi E; Gutierrez L	Zhong X; Gutierrez L (2)	Lockhart MM	Coyle D
Effectiveness: 23	**Outcome: 12**	**Clinical value: 7**	**Cost-effectiveness: 4**		
	Weidenbaum ML; Dockhorn RJ; Dickov V; Morrison C; Murray MD; Winegarden W; Barkan J; Numerof RE; Pauwels K; Zhong X; Garrison LP; Coyle D	Lu ZJ; Zhong X; Numerof RE; Pauwels K; Rollet P; Gutierrez L; Wise J	Morrison C; Calfee JE; Siegelman S; Coyle D		
Cost aspects: 39	**R&D costs: 18**	**Cost of failure: 8**	**Manufacturing costs: 5**	**Cost of capital: 4**	**Regulatory & commercialization costs: 4**
	Vagelos PR; Weidenbaum ML; Calfee JE (2); Dockhorn RJ; Sollano J; Tambuyzer E; Lockhart MM (2); Reinhart R; Zhong X; Davies JE; Numerof RE; Winegarden W; Gutierrez L; Patel KR; Rollet P; Coyle D	Winegarden W; Calfee JE; Sollano J; Lockhart MM; Zhong X; Davies JE; Rollet P, Coyle D	Calfee JE; Tambuyzer E; Lockhart MM; Reinhart R; Winegarden W	Rollet P; Tambuyzer E; Vagelos PR; Zhong X	Tambuyzer E (3); Wise J
Innovational aspects: 17	**New treatments: 6**	**Future research: 6**	**Innovation n.o.d.: 5**		
	Rollet P; Saadi E; Gutierrez L; Winegarden W; Wise J; Weidenbaum ML	Tambuyzer E; Pauwels K; Zhong X; Numerof RE; de Sola-Morales O; Coyle D	Rollet P; Murray MD; Davies JE; Kibble A; Coyle D		
Drug development complexity: 24	**Risks: 14**	**Safety: 5**	**Duration & complexity: 5**		
	Calfee JE; Ruffolo RR, Tambuyzer E (2); Lockhart MM; Zhong X (3); Dickov V; Rollet P; Saadi E (2); Winegarden W; Barkan J	Tambuyzer E; Sollano J; Davies JE; Numerof RE; Dickov V	Tambuyzer E; Zhong X; Dickov V; Saadi E; Gutierrez L		

*For reasons of readability of the table only the first author of the publications included is mentioned. Full disclosure can be found in the reference section.
[a]The number between brackets is the number of different components (sub-elements) that belong to a specific element.

chart in Figure 1 illustrates reasons for exclusion and the number of excluded publications (Moher et al., 2009). All included publications were analyzed for concepts that attributed to the specific value elements and were placed into the framework. Subsequently, when analyzing the concepts in the framework, we identified several sub-elements per element. By grouping the results, we were able to quantify elements and sub-elements and we, thereby, replaced some of the concepts placed in the element 'other' to an already defined element, and subsequently, grouped the remaining concepts placed in the element 'other' and renamed it 'drug development complexity' as displaced in Table 1.

3.2 Societal considerations

Concerning societal considerations–benefits to society –, we grouped the concepts found in literature into five sub-elements. First, seven publications linked value to social or unmet needs (Weidenbaum, 1993; Saadi and White, 2014; Gutierrez et al., 2015; Morrison, 2015), more in detailed described as societies should care for those in need (de Sola-Morales, 2019), or should help to ensure that patients can obtain the medicine they need (Vagelos, 1991; Wise et al., 2018). Secondly, seven publications mentioned quality of life on a population level such as improved

population health (Saadi and White, 2014) and population wellbeing (Wise et al., 2018), reduction of morbidity rate (Siegelman, 1991), reducing disability days and potential years of life lost before the age of 65 (Vagelos, 1991), and long-term benefits for humans (Davies et al., 2012) in general and, specifically, for caregivers and family (Coyle et al., 2020; Garrison et al., 2021). Thirdly, six publications mentioned increased productivity (Vagelos, 1991; Saadi and White, 2014; Wise et al., 2018) and recessed absent from work (Siegelman, 1991; Pauwels et al., 2016) and, in the case of cell and gene therapies, even lifetime productivity (Garrison et al., 2021). A fourth sub element was related to the impact on the national healthcare budget and potential cost savings to society (Coyle et al., 2020) and whether prices were seen as justifiable to payers (Rollet et al., 2013) in accordance with national budgets and priorities (Pauwels et al., 2016). Conversely, in two publications it was mentioned that the burden placed on society was low, stating that innovative drugs only have been making up a small proportion of total healthcare expenditures (Weidenbaum, 1993) and because the number of patients treated with these drugs is low (Tambuyzer, 2010). Lastly, in recent publications the value of especially cell & gene therapies was linked to insurance value, which can be distinguished in two types of risk protection on a population level: physical risk protection (reduced fear of a disease) and financial risk protection (covering cost of treatment through an insurance system) (Postma et al., 2022).

3.3 Economic considerations

With respect to drug price-related economic considerations, we grouped the concepts into four sub-elements: 1) return on investment; 2) willingness-to-pay; 3) country-specific pricing characteristics and 4) competition. In 18 publications drug prices were linked to return on investment. This was described by: i) an appropriate return on research investment (Vagelos, 1991); ii) the basic incentive to make such investments in the possibility of high profits (Weidenbaum, 1993; Calfee, 2001); iii) the hope of someday obtaining large profits from rare success (Calfee, 2001), and iv) making profits in order to be able to continue to reinvest in the developments of new medicines for complex conditions (Tambuyzer, 2010; Rollet et al., 2013). Furthermore, economics of potential drugs were studied upfront (Dockhorn, 2005). A second sub-element was willingness-to-pay, reflected by 13 publications and stated by, e.g., Wise et al. (Wise et al., 2018) as "the pharmaceutical challenge: [the] therapeutics must meet unmet patient needs at a cost that society can afford". Moreover, Coyle et al. stated that "the value of innovative therapies should reflect society's preferences to pay more for greater health gain, health gains for highly debilitating conditions or for survival extension near end-of-life" (Coyle et al., 2020). Furthermore, in one publication it was stated that if societies were willing to pay for value drug prices could differ between different medical indications (Pauwels et al., 2016). Hence, higher value to patients should actually command a higher price (Morrison, 2015). The third sub-element considered country-specific price differences due to price elasticity within a society (Zhong, 2010), variations in government price controls, healthcare financing practices (Vagelos, 1991) or a supportive attitude towards business environment for innovative pharmaceuticals (Wise et al., 2018). Price differences also occurred when prices in one country subsidized prices in another country (de Sola-Morales, 2019) or were due to different outcomes of the value of a drug based on different HTA-technologies and assessment methodologies (Wise et al., 2018). Finally, the fourth sub-element related to competition or lack thereof, in which competition had a dampening effect on drug prices (Lu and Comanor, 1998; Calfee, 2001) and market protection such as market exclusivity or patenting enabled the pharmaceutical industry to recoup costs. Then again, these protection policies were not preventing the marketing of other orphan medicinal products (Rollet et al., 2013). Indeed, companies would anticipate price pressure and price erosion, leading to higher prices at initial price setting (Pauwels et al., 2016). Therefore, the ultimate challenge is to achieve success in the face of shorter patent exclusivity periods and global enforcement of more stringent price controls and reimbursement criteria (Sollano et al., 2008).

3.4 Healthcare process considerations

In almost all publications, a drug's price was related to healthcare process considerations and, specifically, to superior treatment or reduction of other costs of healthcare delivery. Concerning superior treatment, efficacy with comparator products (Zhong, 2010; Silverman, 2013; Gutierrez et al., 2015) and medical and therapeutic advances (Dickov, 2012) were mentioned, especially reduction of surgery (Vagelos, 1991; Weidenbaum, 1993; Winegarden, 2014). Four publications mentioned substitution of a lifetime of medical interventions to a one-time treatment (Morrison, 2015; Coyle et al., 2020; Garrison et al., 2021; Postma et al., 2022) of which three publications were of the last 3 years and specifically regarding cell & gene therapies. According to Coyle *et al.* (Coyle et al., 2020) and Postma et al. (Postma et al., 2022), these therapies, moreover, faced logistic, procedural and treatment challenges for healthcare delivery, including increasing treatment costs. Subsequently, superiority was stated to come at a higher price (Vagelos, 1991; Zhong, 2010). Conversely, the reduction of other healthcare delivery costs, especially reduced hospitalizations, was mentioned in seven publications (Siegelman, 1991; Vagelos, 1991; Murray and Deardorff, 1998; Saadi and White, 2014; Winegarden, 2014; Pauwels et al., 2016; Wise et al., 2018). Three publications mentioned patients' accessibility to innovative therapies to be an important consideration (Vagelos, 1991; Saadi and White, 2014; Gutierrez et al., 2015). Moreover, prices should be kept at reasonable levels, as new therapies were useless if patients could not access them (Vagelos, 1991). Gutierrez et al. added ethical perspectives, such as the rule of rescue or the equity of opportunity for patients to benefit (Gutierrez et al., 2015). In one publication a relationship was found between drug prices and patients' and physicians' preferences (Zhong, 2010).

3.5 Patient characteristics

Patient characteristics were mentioned in six publications and were mostly linked to the heterogeneity of the patient population and to the understanding of the patient population

(Zhong, 2010; Numerof and Abrams, 2012; Rollet et al., 2013; Gutierrez et al., 2015; Barkan, 2019). Scarcity of the available patient pool and the heterogeneous populations made it difficult to identify validated clinical endpoints (Rollet et al., 2013) and, subsequently, forced pharmaceutical companies to develop a deeper understanding of that population's characteristics (Numerof and Abrams, 2012) and to contribute to the value of a patient's hope (Barkan, 2019). The concept of personalized medicine should suggest that many new drugs will only reach a proportion of the patients suffering from a particular disease (Zhong, 2010). In one publication the price of a drug was related to the patient's weight (Morrison, 2015).

3.6 Disease characteristics

Regarding disease characteristics, in 14 publications drug prices were considered to be related to the rarity or severity of the disease and the type of disease. According to several publications, the rarity of the disease was linked to complexity of drug development due to low prevalence (Tambuyzer, 2010; Barkan, 2019), higher unit costs (Davies et al., 2012) and a small number of potential patients (Rollet et al., 2013; Silverman, 2013). Regarding the type of disease, it was mentioned in several publications that drug prices were related to disease heterogeneity (Zhong, 2010), level of knowledge on the disease (Gutierrez et al., 2015), or whether a disease was considered more severe (Gutierrez et al., 2015), more acute (Lu and Comanor, 1998) or was associated with certain perceptions (Saadi and White, 2014), such as inherited diseases or diseases acquired by lifestyle. In one publication, the focus was to find a solution for diseases with insufficient treatment options (Lockhart et al., 2010).

3.7 Effectiveness

Effectiveness in relation to drug prices was mentioned in 23 publications whereas half of the publications described effectiveness as outcome effects, such as extending life expectancy (Dickov, 2012), saving lives (Dockhorn, 2005), or in general improving the quality of a patient's life (Weidenbaum, 1993; Murray and Deardorff, 1998; Dockhorn, 2005; Winegarden, 2014; Morrison, 2015; Pauwels et al., 2016; Barkan, 2019; Coyle et al., 2020). Furthermore, it was stated that actual prices are closely related to a patient's benefit of the treatment (Weidenbaum, 1993; Winegarden, 2014) or to a patient's responsiveness to the treatment (Zhong, 2010). In publications on cell & gene therapy price was related to the benefits of a one-time (Garrison et al., 2021) or non-chronic treatment, thereby lowering the number of hospitalizations or chronic care for patients (Coyle et al., 2020). A second element that referred to effectiveness was clinical value, whereas two publications stated a direct relationship between therapeutic improvement and drug price at market introduction (Lu and Comanor, 1998; Zhong, 2010). Cost-effectiveness was mentioned in four publications, indicating a relation between price and cost-effectiveness (Siegelman, 1991; Morrison, 2015; Coyle et al., 2020) yet one publication was opposed to that, stating that costs of drug development and ultimate benefits of that drug are not necessarily related (Calfee, 2001).

3.8 Costs

Almost all publications mentioned cost aspects in relation to drug pricing, which were grouped into five sub-elements. First, most publications mentioned cost for R&D, indicating that cost of R&D is a major factor in determining the price of a new drug, including the cost for discovering a new drug (Dockhorn, 2005; Lockhart et al., 2010; Patel, 2017; Coyle et al., 2020). Especially clinical trials place a great burden on R&D costs (Weidenbaum, 1993; Dockhorn, 2005; Lockhart et al., 2010; Tambuyzer, 2010; Davies et al., 2012; Rollet et al., 2013; Winegarden, 2014). Therefore, drug prices should allow for companies to recoup their R&D costs (Reinhart and Modrzjewski, 2010; Zhong, 2010; Gutierrez et al., 2015). Furthermore, in addition to cost of R&D, cost of failures was mentioned (Calfee, 2001; Sollano et al., 2008; Lockhart et al., 2010; Zhong, 2010; Davies et al., 2012; Winegarden, 2014; Coyle et al., 2020). Rollet et al. (Rollet et al., 2013) stated that "the proportion of failures is the most important driver for R&D costs", whereas Calfee (Calfee, 2001) argued to "bear in mind research failures and bankruptcies that may have proceeded the creation of a financially successful new drug". Third, cost of production and manufacturing was mentioned in five publications (Calfee, 2001; Lockhart et al., 2010; Reinhart and Modrzjewski, 2010; Tambuyzer, 2010; Winegarden, 2014). Fourth, four publications mentioned cost of capital (Vagelos, 1991; Tambuyzer, 2010; Zhong, 2010; Rollet et al., 2013) and finally, two publications touched upon the regulations and commercialization costs (Tambuyzer, 2010; Wise et al., 2018).

3.9 Innovation

Murray and Deardorff stated (Murray and Deardorff, 1998) that "innovation is the lifeblood of the pharmaceutical industry" and it is, therefore, argued that the business models of pharmaceutical companies are associated with high prices to counterbalance the large focus on innovation (Rollet et al., 2013). Making a profit is considered to be an important driver for further research and offers possibilities for investing in future pipelines and tomorrow's medicines (Tambuyzer, 2010; Rollet et al., 2013; Pauwels et al., 2016; de Sola-Morales, 2019). Moreover, the value of innovation is important because of the scientific spill-over effect: knowledge gained from one drug leads to the development of other valuable innovations (Coyle et al., 2020). Furthermore, limiting prices of drugs could have a negative impact on innovation and could result in not being able to fulfill unmet needs of patients (Kibble & D'Souza, 2015; Weidenbaum, 1993; Winegarden, 2014; Wise et al., 2018).

3.10 Drug development complexity

The last element–drug development complexity–was composed of the sub-elements risks, safety, and complexity. Most publications

TABLE 2 Hierarchy of elements to consider in value-based pricing from a pharmaceutical industry's perspective.

Economic considerations	Cost aspects	Healthcare process considerations	Societal considerations	Drug development complexity	Effectiveness	Innovational aspects	Disease characteristics	Patient characteristics
Return on investment Willingness-to-pay Country-specific pricing characteristics Competition	R&D costs Cost of failure Manufacturing costs Cost of capital Regulatory & commercialization costs	Superior treatment Reduction other cost of healthcare delivery Patient access Preferences Logistics & treatment challenges	Unmet or social needs Quality of life on population level Increased productivity Impact on healthcare budget Insurance value	Risks Safety Duration & complexity	Outcome Clinical value Cost-effectiveness	New treatments Future research Innovation	Disease rarity Type of disease Disease heterogeneity Other treatment options Disease severity	Patient heterogeneity Knowledge of patient population Personalized medicine

TABLE 3 Hierarchy of elements after sensitivity analysis.

Economic considerations	Cost aspects	Societal considerations	Healthcare process considerations	Drug development complexity	Effectiveness	Disease characteristics	Innovational aspects	Patient characteristics
Return on investment Willingness-to-pay Country-specific pricing characteristics Competition	R&D costs Cost of failure Manufacturing costs Cost of capital Regulatory & commercialization costs	Unmet or social needs Quality of life on population level Increased productivity Impact on healthcare budget Insurance value	Superior treatment Reduction other cost of healthcare delivery Patient access Preferences Logistics & treatment challenges	Risks Safety Duration & complexity	Outcome Clinical value Cost-effectiveness	Disease rarity Type of disease Disease heterogeneity Other treatment options Disease severity	New treatments Future research Innovation	Patient heterogeneity Knowledge of patient population Personalized medicine

10.3389/fphar.2024.1298923

mentioned risks to be included in drug pricing. As Tambuyzer (Tambuyzer, 2010) stated "the price of a drug and the corresponding cost per patient is determined by the risk taken to develop the product, which is reflected in the profit potential". Drug development was considered to be a high risk industry (Ruffolo, 2005) from several perspectives such as high risk levels of the R&D process and failure rates (Lockhart et al., 2010; Zhong, 2010; Dickov, 2012; Saadi and White, 2014; Barkan, 2019), unique risks reflected by frequent mergers and acquisitions (Zhong, 2010), increase of unprecedented drug withdrawals and product liability lawsuits (Zhong, 2010), structural hurdles contributing to an increased risk of failure (Rollet et al., 2013), and risks inherent to commercial success and adequate return on investment (Saadi and White, 2014; Winegarden, 2014). A second sub-element was safety in which the ultimate challenge is to achieve success in the face of increasing demands, i.e., increasing regulatory hurdles for evidence of safety and efficacy (Sollano et al., 2008; Davies et al., 2012; Numerof and Abrams, 2012). Finally, in five publications it was considered the complexity and duration of the entire process of drug development (Tambuyzer, 2010; Zhong, 2010; Dickov, 2012; Saadi and White, 2014; Gutierrez et al., 2015) to be reflected in the price.

3.11 Summary of covered elements

We found nine different elements, and we grouped several sub-elements per element (see Table 2). The order of the elements resembles how often an element was mentioned in the included publications and is, therefore, considered an indication of the hierarchy of the elements. In order of importance: 1) economic considerations; 2) cost aspects; 3) healthcare process considerations 4) societal considerations; 5) drug development complexity; 6) effectiveness; 7) innovation; 8) disease characteristics; and 9) patient characteristics. The sensitivity analysis in which eight articles (25%) were excluded that were not reviews or analyses (i.e., conference summary, special report, editorial, news, magazine article, report, case report) revealed a slight change the elements hierarchy in which healthcare process consideration and societal considerations switched, as well as innovation and disease characteristics: (1) economic considerations; 2) cost aspects; 3) societal considerations; 4) healthcare process considerations 5) drug development complexity; 6) effectiveness; 7) disease characteristics; 8) innovation; and 9) patient characteristics). The patient characteristics element diminished from 9 times to 5 times mentioned (a 55% reduction). Economic and cost considerations remained in the same position (Table 3). Lastly, we analyzed the order of the elements over time. In publications appeared in the period from 1991 to 2000 societal and healthcare process considerations were more prominently present, whereas publications appeared between 2001 and 2010 were more focused on business aspects, such as costs, economic considerations and drug development complexity. From 2011 up to 2022 the focus was on a combination of business and societal aspects. However, throughout the years patient and disease characteristics were not among the top five of considered elements of value (Table 4).

4 Discussion

4.1 Key findings

The aim of our study was to identify the elements that attribute to value-based pricing of innovative drugs from a pharmaceutical industry's perspective, in an attempt to resolve the controversy over transparency on drug prices and contribute to a jointly defined and agreed upon framework for value-based pricing as a starting point for value-based contracting.

Reviewing the 31 included publications, we found that all elements that were placed into our framework were covered. Assuming that the emphasis placed or not placed on elements determining the value of innovative drugs was indicated by the number of times these elements appeared in the analyzed publications, our study resulted in the following three key findings.

First, economic considerations and cost aspects associated with the development, registration, manufacturing and marketing of innovative drugs are the two most frequently mentioned elements for establishing a price. Furthermore, innovation, disease characteristics and patient characteristics were least mentioned in relation to value-based pricing. Secondly, effectiveness and, more specifically, cost-effectiveness, being an important parameter of traditional HTA decisions, were hardly mentioned in the reviewed publications. However, healthcare process and societal considerations, likewise important elements of drug value framework preceded cost-effectiveness. And finally, the complexity of drug development should be added as an additional element to drug value.

Regarding the first key finding, our results supported the unexpected importance of economic and cost aspects regarding determination of prices of innovative drugs. Especially considering the pharmaceutical industry's emphasis on a broader concept of value and their reluctance to cost-based pricing. Gregson's methodological framework of pricing basics underlined our results. Pricing is a trade-off in which the manufacturer sets the lowest price considering costs and profit and the market sets the upper limit price through a maximum of willingness-to-pay (Gregson et al., 2005b). Nevertheless, in a systematic review by Morgan et al. (Morgan et al., 2011) it was concluded that no 'golden standard' was available to estimate the cost of developing a drug. Additionally, Lexchin argued that "drugs are being priced on how desperate patients are, not how much it costs to develop them" (Lexchin, 2017).

Regarding the second key finding, effectiveness and, especially cost-effectiveness, does not qualify as an important element of value-based pricing, except for effectiveness in terms of contributing to outcome, convenience, superiority of the new treatment or reducing other healthcare costs. Moreover, our results demonstrated little or even reverse attention of cost-effectiveness in relation to a drug's value. Since cost-effectiveness is an important parameter in determining value and, eventually, price in many countries, payers and industry seem miles apart.

This finding was confirmed by several studies in which no relationship was found between price and therapeutic improvement (Suslow, 1992; Vogler and Paterson, 2017). In more recent studies no evidence of a strong relationship was found between effectiveness and the price of orphan drugs or cancer drugs (Onakpoya et al., 2015). However, nowadays, in many countries it is common practice to determine the prices of new innovative drugs, at least partly, based

TABLE 4 Hierarchy of elements over time.

1991 - 2000	2001–2010	2011–2022
Societal considerations (7)	Cost aspects (22)	Societal considerations (22)
Healthcare process considerations (7)	Economic considerations (14)	Economic considerations (20)
Economic considerations (6)	Drug development complexity (12)	Healthcare process considerations (20)
Effectiveness (4)	Effectiveness (4)	Effectiveness (15)
Cost aspects (3)	Healthcare process considerations (4)	Cost aspects (14)
Innovational aspects (2)	Disease characteristics (3)	Innovational aspects (13)
Disease characteristics (1)	Patient characteristics (2)	Drug development complexity (12)
Patient characteristics (0)	Innovational aspects (2)	Disease characteristics (10)
Drug development complexity (0)	Societal considerations (1)	Patient characteristics (7)

on HTA, cost-effectiveness analysis (CEA) or determination of the incremental cost-effectiveness ratio (ICER) (Vogler et al., 2017). Nevertheless, in the case of the latest cell and gene therapies traditional cost-effectiveness analysis is deemed not appropriate (Coyle et al., 2020).

Simultaneously, pressure on the healthcare system in developed countries is increasing. Time has come that pharmaceutical companies should move forward and should be forced to be more transparent. Shareholders can play an important role and should raise their voices to impose a sustainable and socially responsible business that creates value to all stakeholders.

As mentioned before, in 2020 the EFPIA introduced novel pricing methods that build on effectiveness and outcomes (EFPIA, 2020). Hence, nowadays more attention is given to this element than we found in our research. A recent study by Villa et al. revealed no strong relation between the epidemiology–incidence or prevalence–of rare diseases and their cost of treatment (Villa et al., 2022). Nevertheless, as concluded by Neumann et al., mutual starting points are on valuing the societal and healthcare process benefits of pharmaceuticals (Neumann et al., 2021).

Lastly, regarding drug development complexity, we found that Hughes-Wilson et al. stated that manufacturing complexity, and the level of research undertaken should be part of the evaluation framework of orphan drugs (Hughes-Wilson et al., 2012).

For now, it is important to continue raising awareness on the subject and keep conducting research to quantify and weigh the elements that constitute value. Moreover, it is important that health authorities who establish the maximum price of innovative drug and representatives of pharmaceutical companies agree on which value elements are important to consider in the eventual price. With upcoming one-time treatments in gene and cell therapy it is even more important, because effectiveness and cost-effectiveness may not be sufficient parameters for these treatments in the future, whereas (long term) societal and healthcare benefits may even become more relevant. The same applies to the increasing complexity of drug making of the cell and gene therapies and the complex and personalized ways of drug preparation and administration. Maybe because of these long term and unforeseeable benefits (or risks) and increased complexity a cost-based-plus model might in the end be a solution, whereas the plus can be profit, complexity or any other elements from this review all parties agree upon.

4.2 Limitations

Our review has some important limitations. First, it was based on a systematic search of publications in scientific platforms, such as PubMed, Econlit and Embase, and omitted the debate and public statement in publications in more popular magazines, newspapers or pharmaceutical companies' websites. Furthermore, we did not weigh the elements, instead, we valued them according to the number of times they appeared in journals. Finally, we focused on innovative drugs, thereby not paying attention to value changes over time–i.e., at market introduction, after market entry of competitive alternatives or patent expiry. Furthermore, we considered all elements separately with less attention to possible interlinkages of different elements. For instance, innovation is an element of value, but as mentioned in the introduction paragraph, it is related to, e.g., public health, social and economic needs, or healthcare process convenience considerations. More research is required to prioritize and quantify the weights and dependency of all relevant elements, and to weigh these elements over time. Moreover, it is valuable to search for additional elements of value that have gained more attention currently, such as sustainable production, effectiveness related to gender and fair distribution and availability of drugs.

4.3 Conclusion

Although we found similar elements that attribute to the value of innovative pharmaceuticals, both from payers' or health authorities' and pharmaceutical industry's perspectives, finding common ground for agreed upon elements seems very complicated, especially considering the element of (cost-)effectiveness which is an important part of the existing drug value frameworks.

While understandable that cost aspects and economic considerations play an important part in drug pricing, considering the commercial field pharmaceutical companies operate, their prominent presence in publications on the value of innovative drugs was not expected and, therefore, remarkable. Therefore, mutual starting points may be found in the value elements on societal considerations and healthcare process benefits potentially linked to innovation, and the

acknowledgement of drug development complexity. Especially because in the last 10 years the order of elements resembles the increasing importance of societal and healthcare process aspects in addition to business considerations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

AD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing–original draft, Writing–review and editing. CU-dG: Data curation, Formal Analysis, Supervision, Writing–review and editing. HK: Data curation, Formal Analysis, Supervision, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors wish to thank Wichor Bramer PhD, Medical Library Erasmus MC, for developing the initial search strategy and Elise Krabbendam MSc, Medical Library Erasmus MC, for conducting the updated database search, Florentine Hogenhuis MSc, Department of Hospital Pharmacy Erasmus MC, for independently analyzing the included articles in the first search and Anne-Sophie Klein Gebbink MSc, Department of Hospital Pharmacy Erasmus MC, for support with screening articles on title and abstract of the updated search.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1298923/full#supplementary-material

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