frontiers | Frontiers in Oncology

TYPE Clinical Trial
PUBLISHED 10 June 2025
DOI 10.3389/fonc.2025.1577468

OPEN ACCESS

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RECEIVED 15 February 2025
ACCEPTED 12 May 2025
PUBLISHED 10 June 2025

CITATION
Fontenot R, Biyani N, Bhatia K, Ewesuedo R, Chamberlain M and Sharma P (2025) Clinical outcomes of DNA-damaging agents and DNA damage response inhibitors combinations in cancer: a data-driven review.
Front. Oncol. 15:1577468.
doi: 10.3389/fonc.2025.1577468

Clinical outcomes of DNA-damaging agents and DNA damage response inhibitors combinations in cancer: a data-driven review

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The combination of DNA-damaging agents (DDAs) and DNA damage response inhibitors (DDRis) has been extensively studied to improve therapeutic outcomes. While both groups of agents show promise individually, DDAs are limited by tumor resistance, and DDRis are limited by specific genetic context. Combining DDAs with DDRis may overcome these challenges and enhance patient outcomes. This review systematically analyzes clinical trials investigating the combination of DDAs and DDRis by dividing them into two sections: PARP and non-PARP inhibitors. An evaluation was conducted on 221 DDA-DDRi combination-arm trials involving 22 DDAs and 46 DDRis. DDAs were classified into eight subclasses, and DDRis into 14 distinct subclasses based on their mechanisms of action and specific targets, respectively. 89 of the 221 combination-arm trials had interpretable outcomes and were selected for further analysis. These were assigned outcome scores based on predefined criteria, reflecting their clinical effectiveness, safety, and benefit across different tumor types and patient populations. Our analysis emphasizes the patterns in treatment effectiveness, safety, and emerging trends across various cancer types and discusses the potential of biomarkers to guide treatment selection and improve patient outcomes. This review outlines an understanding of the recent state of DDA-DDRi combinations, offering critical insights for refining future cancer treatment strategies.

KEYWORDS

DNA-damaging agents, DNA damage response inhibitors, PARP inhibitors, combination therapy, clinical trials, DNA repair pathways, cancer treatment, biomarkers

1 Introduction

DNA-damaging agents (DDAs), including chemotherapy and radiotherapy, have long been central to cancer treatment. They rely on their ability to induce irreparable genetic damage in rapidly dividing tumor cells (1). However, the efficacy of DDAs is frequently hampered by the activation of DNA damage response (DDR) mechanisms in cancer cells, which enable DNA repair and promote cell survival (2). This has spurred the development of DDR inhibitors (DDRis) designed to target these repair mechanisms, thereby enhancing the cytotoxic effects of DDAs (2, 4).

The DDR network is a complex, interconnected system with redundant pathways that provide compensatory and alternative repair mechanisms (5, 6). This redundancy presents therapeutic opportunities, exemplified by poly (ADP-ribose) polymerase inhibitors (PARPis), which exploit synthetic lethality to selectively kill cancer cells with defective DNA repair, as in cancers with BRCA mutations (3). PARPi approvals for treating ovarian, breast, and prostate cancers marked a significant advancement in personalized cancer therapy (7–11). However, the clinical utility of PARPis is confined mainly to specific genetic contexts, highlighting the need for broader treatment strategies (3). This need has driven the development of next-generation DDRis targeting diverse components of the DDR network.

Inhibitors of ATM, ATR, WEE1, and DNA-PK, for instance, disrupt distinct aspects of the DDR pathway, including cell cycle checkpoint regulation, DNA damage signaling, and repair processes (5, 12, 13). These agents offer potential therapeutic benefits across a broader range of tumor types, independent of specific genetic alterations like homologous recombination (HR) deficiencies, offering a more inclusive approach to overcoming resistance to DNA-damaging therapies (12). However, as monotherapies, DDRis often demonstrate limited efficacy due to rapid adaptation and developing resistance mechanisms in cancer cells (14).

The combination of DDRis and DDAs offers a compelling strategy to overcome these limitations. By simultaneously inducing DNA damage and inhibiting its repair, this approach can circumvent resistance mechanisms observed with monotherapy and expand the therapeutic potential beyond traditional DDA applications (2, 15). Numerous clinical trials are investigating these combination strategies across various cancer types and treatment regimens. The success of these combinations is influenced by factors such as tumor type, genetic profile, and the specific agents used. A critical challenge lies in identifying predictive biomarkers that can stratify patients based on their likelihood of response, enabling personalized treatment strategies and minimizing unnecessary toxicity (13, 16).

This review systematically analyzes the results of 221 DDAs-DDRis combination-arm clinical trials, encompassing 22 DDAs and 46 DDRis, without employing statistical methods. DDAs were grouped into eight subclasses according to their mechanisms of action, while DDRis were classified into 14 subclasses based on their specific targets. From the 221 initial combination-arm trials, 89 with interpretable outcomes were selected for in-depth analysis. These 89 trials were scored based on predefined criteria evaluating clinical effectiveness, safety, and benefit across diverse tumor types and patient populations, incorporating biomarker data where available. Given the prominent role of PARPis, the review is divided into PARP-focused and non-PARP-focused sections. By analyzing successful and challenging regimens, this work aims to provide a comprehensive overview of the field and inform future research on refining these combined therapies.

2 Methods

The identification of relevant clinical trials and assembly of trial details and outcomes relied on accessing and organizing information from clinicaltrials.gov in conjunction with internally developed python scripts as well as steps of manual review and annotations to ensure details of each trial, drug, and results are reliable and accurate. Figure 1 includes an overview of the workflow, and detailed descriptions of workflow sections follow.

2.1 Clinical trial data acquisition and processing

A queryable database of clinical trial information was needed to identify applicable trials and the relevant information associated with each trial. Pytrials (https://pytrials.readthedocs.io/en/latest/) provides a python query tool using the Clinicaltrials.gov API (https://clinicaltrials.gov/data-api/api); however, the API does not include relevant sections such as the trial's detailed description, patient inclusion criteria, PMID references discussing trial results, and many more fields available on the clinicaltrials.gov page for each trial. Furthermore, the interventions returned by the API require further processing to properly extract and separate drug names.

In addition to the API clinicaltrials.gov allows users to download a JSON file including all fields for all trials. Data can be downloaded from this link: https://clinicaltrials.gov/search by clicking on the download button and selecting JSON with all available fields.

The nested trials inside the downloaded JSON are text rather than standardized dictionaries and do not all have the same fields or formats. A custom python script with additional processing was created to transform the JSON file into a standardized data table containing all fields available for each trial.

While the clincaltrials.gov page and JSON for each trial include a list of treatments in the "interventions" section, in many cases, it is not a complete list of drugs in the trial or synonyms the drug name is referenced to throughout the trial documents. Scripts using natural language processing and regular expressions tools were created to extract all drug names from the Interventions, ARM-Groups, and ARM-Interventions fields and compiled into a complete list for each trial in the newly created database.

The clinicaltrials.gov pages and downloads do not specifically include a field or label indicating whether the trial is a drug combination trial, so a rules-based script was created to flag

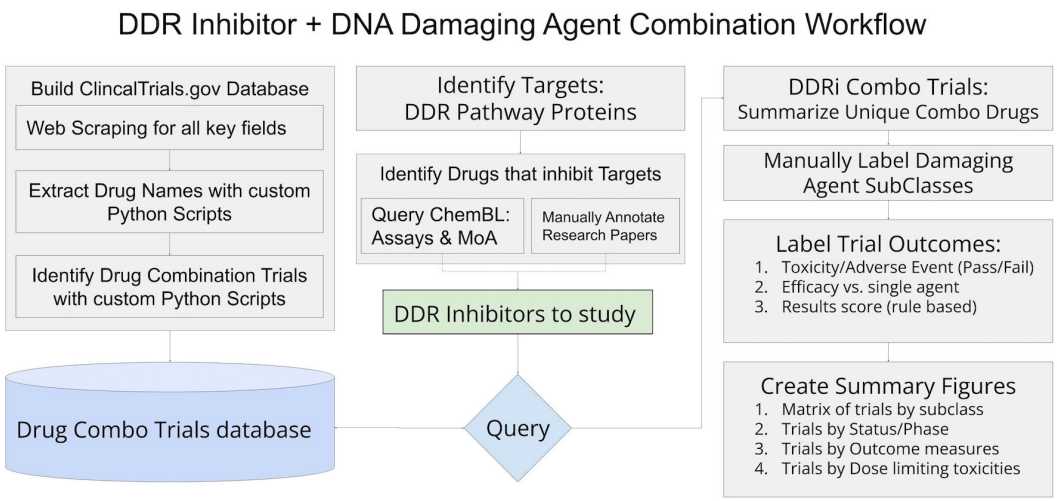

FIGURE 1
Workflow diagram of methods utilized to assemble data and results for this study.

which trials are drug combination trials. If a trial includes more than one drug, it is not necessarily a drug combination trial as the drugs may be administered as monotherapies for comparison in different arms of the trial. A rules-based script using natural language processing and regular expressions was created to flag trials with the words "combination" or "combined" used in either the trials title or brief summary and more than one unique drug in the trial drugs list created as described above. These flagged trials were included in a drug combinations specific view of the database for downstream querying and analysis. In total 490,490 clinical trials were processed, and 31,576 trials were identified as drug combination trials.

2.2 DNA damage repair inhibitor and DNA damaging agent identification

Identification of drugs that inhibit DDR pathways was accomplished by two methods, assay research and reviews of public conference presentations. A list of 120 proteins involved in the HR, NHEJ, alt-NHEJ, NER, MMR, BER, ICL, and TLS DNA damage repair pathways was compiled from literature (5, 17–31) to query the ChemBL database (https://www.ebi.ac.uk/chembl/). The query searched for inhibition assays for each protein in the compiled list and joined the drug names and drug name synonyms for each study with a significant percentage inhibition of the applicable protein and its associated repair pathway to retain the subclass of DNA damage repair inhibitors.

The list of 46 DDRis identified was used to query the drug combination clinical trials database view, resulting in 1,549 trials for initial review. A list of all unique drug names included in these trials resulted in 731 drugs that were manually annotated as DDA vs. other classes of drugs. Twenty-two DDAs across eight different DNA-damaging subclasses were identified as having at least one trial in combination with a DDRi. After filtering initially identified trials to the applicable drug class combinations, 221 trials with a DDRi and DDA in combination were identified for full review, with 89 of the trials being complete with at least one public source of the trial outcomes.

During the trial review phase, additional trials were removed as not relevant to this study if the DDA is only in a comparator arm while the DDRi drug was in a separate experimental arm rather than a test in combination.

In trials with multiple arms containing a DDRi + DDA combination, each arm was evaluated separately during reviews. This format allows for the analysis of counts based on specific drug combinations rather than a trial study ID.

2.3 Assigning numerical scores based on trial outcomes

Each applicable trial with results was manually reviewed to summarize outcomes from both outcome measures reported on clinicaltrials.gov tables as well as publicly available research papers summarizing results. For the purposes of visualization figures to graphically summarize which combinations of drug classes and specific drugs have demonstrated positive outcomes vs. negative or inconclusive outcomes, a numerical score was assigned to each trial. This numerical score is utilized to color code figures for a high-level representation of outcomes covering multiple trials as introduction prior to presenting details on specific individual trials or drug classes.

Initially three categories of numerical scores assigned are based on the following criteria during the manual annotation of outcomes process:

2.3.1 Toxicity score

Trials that were discontinued due to significant adverse events or toxicities that prevented trial completion were graded as a

negative outcome and assigned a numerical score of 1 representing the occurrence of discontinuation due to toxicity. Trials that were able to complete the study without trial limiting adverse events were graded as positive and assigned a score of 0, representing the lack of discontinuation. Although trials that received a score of 0 reported adverse events of varying severity, the current scoring system does not differentiate between the levels of severity of these adverse events, and no additional scoring was implemented to address this.

2.3.2 Overall efficacy score

In trials where outcomes were measured as defined endpoints, the most used efficacy endpoints included partial response (PR), complete response (CR), objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), and overall survival (mOS), disease (SD), duration of response (DoR). Combination-trial arms achieving predefined efficacy endpoints were graded as positive outcome and assigned a numerical score of 1 (positive efficacy); those failing to meet endpoints were graded as negative and assigned a numerical score of 0 (lack of required efficacy). For trials lacking pre-defined endpoints but reporting efficacy outcomes, results were compared to standard-of-care expectations for the relevant indications and scored in the same manner as trials with defined endpoints. No reported outcomes: Completed combination-arm trial lacking any reported efficacy outcomes (e.g., some maximum tolerated dose [MTD] studies, which often focus on dose-limiting toxicity [DLT] and determining the recommended phase 2 dose [RP2D] rather than direct efficacy) were classified as having no available outcome data.

2.3.3 Biomarker response score

In addition to the overall efficacy score, which is based on all trial participants, combination trial arms that reported differential efficacy outcomes for a subpopulation with specific biomarkers were also graded. Combination trial arms with a biomarker-defined patient subpopulation achieving the trials' predefined efficacy endpoints or meeting standard-of-care expectations were graded as positive and assigned a score of 1. Combination trial arms where the biomarker-defined patient subpopulation did not exceed response rate of the overall trial participant group, or did not have outcomes reported for a biomarker patient subpopulation were graded as neutral and assigned a numerical score of 0.

2.3.4 Outcome score

For use in summary visualizations and figures, these three individual categorical scores were then combined into an overall Outcome Score calculated as:

$$Outcome\ \ Score = Overall\ \ Efficacy\ \ Score + \frac{Biomarker\ \ response\ \ Score}{2}$$

Outcome Score values can be interpreted as:

Score 0: The combination-arm trial had a negative outcome where either the trial was discontinued due to adverse events or toxicities, or when the outcome was negative due to a lack of efficacy.

Score 0.5: The combination-arm trial was not discontinued due to adverse events or toxicities. While efficacy was not demonstrated for the overall participant group, there was a biomarker defined subpopulation that demonstrated efficacy.

Score 1.0: The combination-arm trial was not discontinued due to adverse events or toxicities and demonstrated efficacy for the studied participant group, but there were no outcomes reported for biomarker defined subgroups or the defined biomarker subgroup did not demonstrate efficacy above the other patients in the trial-arm.

Score 1.5: The combination-arm trial was not discontinued due to adverse events or toxicities and demonstrated efficacy for both the studied participant group, as well as an additional improvement in efficacy for a biomarker defined subgroup of participants.

3 Results

3.1 Clinical trial status of DDRis and DDAs: trends, development stages, and trial distribution

To assess the clinical landscape of DDAs-DDRis combinations, we analyzed clinical trials involving 22 unique DDAs in combination with 46 distinct DDRis. As a first step 22 DDAs were classified based on their mechanism of DNA damage into eight distinct DNA-damaging subclasses: alkylating agents, interstrand cross-linkers (ICLs), topoisomerase inhibitors, DNA intercalators, (dual-action agents) DNA intercalation & topoisomerase inhibition, ribonucleotide reductase inhibitors, G-quadruplex stabilizers, and multiple agents (Table 1A). Multiple agents denote a combination of multiple distinct therapeutic regimens, with at least one of these regimens including a DDA, with the possible addition of other agents like paclitaxel or pemetrexed. 46 DDRis were categorized into 14 subclasses based on their specific targets: ATR, AURK, CHK1/2, DNA-PK, PARP, PKMYT1, PLK, PLK+WEE1 (dual-targeting agents), PRMT5, RAD52, TP53, USP1, WEE1, and WRN (Table 1B).

Next, we analyzed clinical trials investigating combinations of these 22 DDAs and 46 DDRis. Each unique DDA-DDRi pairing within a trial was treated as an individual combination-arm trial. This means that if a single trial evaluated multiple treatment arms with different combinations of the DDA-DDRi, each arm was counted separately. The process yielded 221 combination-arm trials for analysis, listed in Supplementary Tables S1, S2 (32–95), and S3.

Clinical trial data, seen in Figure 2, reveals a distinct trend in investigating DDAs-DDRis combinations by plotting the number of tested combinations across all trial phases and recruitment statuses wherein PARPis have been more extensively studied in combination

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TABLE 1A List of DDAs and their Subclasses.

Damaging Drug Name	Damaging class
cyclophosphamide	alkylating agent
dacarbazine	alkylating agent
lurbinectedin	alkylating agent
temozolomide	alkylating agent
trabectedin	alkylating agent
mitomycin c	alkylating agent
doxorubicin	DNA intercalation
daunorubicin	DNA intercalation & topoisomerase inhibitor
epirubicin	DNA intercalation & topoisomerase inhibitor
idarubicin	DNA intercalation & topoisomerase inhibitor
mitoxantrone	DNA intercalation & topoisomerase inhibitor
cytarabine	DNA intercalation, topoisomerase inhibitor
pidnarulex	G-quadruplex stabilizer
carboplatin	Interstrand cross linker
cisplatin	Interstrand cross linker
oxaliplatin	Interstrand cross linker
gemcitabine	Ribonucleotide reductase inhibitor
hydroxyurea	Ribonucleotide reductase inhibitor
ep0057	topoisomerase inhibitor
etoposide	topoisomerase inhibitor
irinotecan	topoisomerase inhibitor
topotecan	topoisomerase inhibitor

TABLE 1B List of DDRi Drugs, Their Subclasses, and affected DNA Damage Response Pathways.

Drug Name	DDRi Subclass	DNA damage response affected by DDRi Subclass
berzosertib	ATR	DNA damage checkpoint
elimusertib	ATR	DNA damage checkpoint
gartisertib	ATR	DNA damage checkpoint
sc0245	ATR	DNA damage checkpoint
tuvusertib	ATR	DNA damage checkpoint
alisertib	AURK	DNA damage checkpoint
chiauranib	AURK	DNA damage checkpoint
ilorasertib	AURK	DNA damage checkpoint
azd7762	CHK1/2	DNA damage checkpoint
prexasertib	CHK1/2	DNA damage checkpoint
rabusertib	CHK1/2	DNA damage checkpoint
sra737	CHK1/2	DNA damage checkpoint
azd7648	DNA-PK	DSBR
peposertib	DNA-PK	DSBR
samotolisib	DNA-PK	DSBR
vx-984	DNA-PK	DSBR
azd5305	PARP	SSBR
cep-9722	PARP	SSBR
e7016	PARP	SSBR
e7449	PARP	SSBR
fluzoparib	PARP	SSBR
nesuparib	PARP	SSBR
niraparib	PARP	SSBR
nms-03305293	PARP	SSBR
olaparib	PARP	SSBR
pamiparib	PARP	SSBR
rucaparib	PARP	SSBR
senaparib	PARP	SSBR
talazoparib	PARP	SSBR
veliparib	PARP	SSBR
venadaparib	PARP	SSBR
rp-6306	PKMYT1	DNA damage checkpoint
bal0891	PLK	DNA damage checkpoint
onvansertib	PLK	DNA damage checkpoint
rigosertib sodium	PLK	DNA damage checkpoint
adavosertib	PLK+WEE1	DNA damage checkpoint
volasertib	PLK+WEE1	DNA damage checkpoint
amg 193	PRMT5	DNA damage checkpoint
gossypol	RAD52	DSBR
idasanutlin	TP53	DNA damage checkpoint
navtemadlin	TP53	DNA damage checkpoint
siremadlin	TP53	DNA damage checkpoint
ro7623066	USP1	TLS and FA
azenosertib	WEE1	DNA damage checkpoint
debio 0123	WEE1	DNA damage checkpoint
hro761	WRN	DSBR and SSBR

SSBR, Single-Strand Break Repair, DSBR, Double-Strand Break Repair, TLS, Translesion Synthesis, FA, Fanconi Anemia.

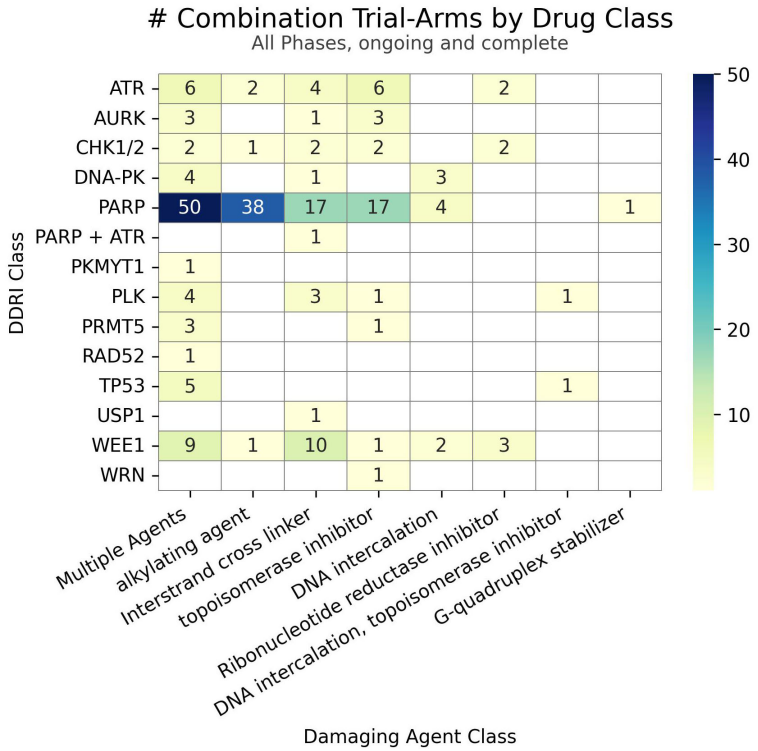

FIGURE 2
The number of combinations tested in trials for each class of DDRi (y-axis) versus DDA (x-axis). Unique drug combinations with multiple trials/phases are counted in the totals. Each drug combination is counted separately under the appropriate drug class totals for trials with multiple arms of interest.

with DDAs. Specifically, 127 combination arms have explored PARPi-DDA combinations, representing 57% of DDAs-DDRis combinations. At the same time, 94 trials have focused on non-PARP inhibitors (non-PARPis) and DDAs combinations, representing 43% of DDAs-DDRis combinations. Among DNA-damaging mechanisms investigated in DDRis combination-arm trials, multiple-agent regimens appeared the most frequently in 88 combination-arm trials. Among single-DDAs combinations with DDRis, alkylating agents were the most commonly investigated (42 combination-arm trials), followed by ICLs (40 combination-arm trials) and topoisomerase inhibitors (32 combination-arm trials). ICL agents, such as carboplatin, cisplatin, and oxaliplatin, are the most frequently utilized DDAs in multi-agent combination studies. The carboplatin and paclitaxel regimen (n=23) is the most commonly used DDAs-DDRis combination in multiple-agent combination arm trials, followed by the cisplatin and gemcitabine regimen (n=7), as shown in Figure 3.

A detailed discussion about multiple agent combination-arm trials is beyond the scope of this article; however, essential information is provided in tables and relevant sections where applicable. Our analysis of the distribution of combination agents by clinical development stage within the PARPi and non-PARPi spaces revealed distinct trends as shown in Figure 4. A greater diversity of combination trials was observed in the PARPi space (Figure 4A). Specifically, among single DDA classes combined with PARPis, alkylating agents were the most frequently investigated in 38 combination-arm trials, followed by ICLs and topoisomerase inhibitors each in 17 combination-arm trials. Conversely, in the non-PARPi space (Figure 3B), ICLs (23 combination-arm trials) and topoisomerase inhibitors (15 combination-arm trials) were more extensively evaluated than alkylating agents (4 combination-arm trials). Alkylating agent combination arms represent 30% of PARPis combination-arm trials compared to 4% of non-PARPi combination arms. In contrast, ICLs were more frequently used in non-PARPi combination-arm trials (24%) than in PARPi combination-arm trials (13%). This indicates a distinct difference in combination strategies, where PARPi primarily combines with alkylating agents, whereas non-PARPi favors a combination with ICL agents.

221 DDAs-DDRis combination-arm clinical trials were distributed as follows: Phase 1 (117), phase 1/2 (49), phase 2 (52), with one in phase 2/3 and two in phase 3. PARPi combination-arm clinical trials were distributed as follows: Phase 1 (62), phase 1/2 (27), phase 2 (35), one in phase 2/3, and two in phase 3. Non-PARPi combination-arm clinical trials were predominantly distributed in Phase 1 (55), followed by phase 1/2 (22) and phase 2 (17), as shown in Figures 5A–D.

3.2 Clinical outcome scoring of selected DDAs-DDRis combination trials in PARPi and non-PARPi spaces

To assess the clinical outcomes of DDAs-DDRis combinations, 89 of the 221 identified combination-arm trials with interpretable

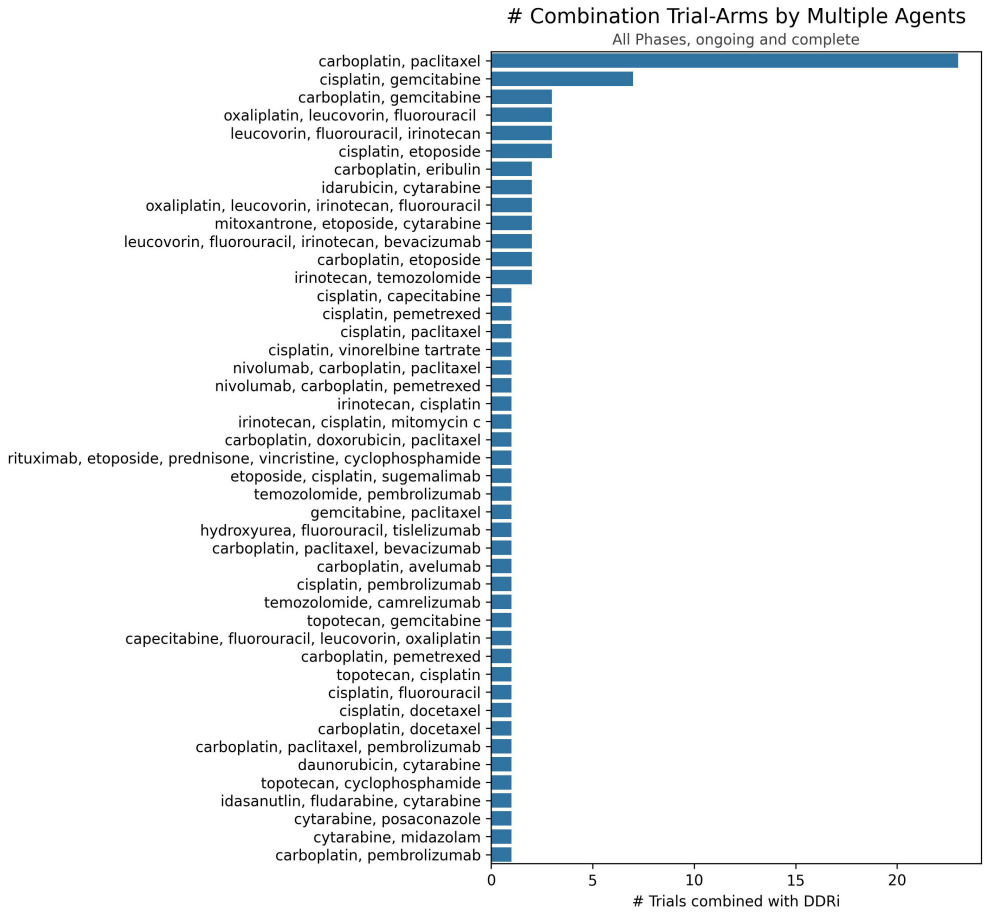

FIGURE 3
Number of trials investigating specific multiple-agent regimens in combination with DDRis. The x-axis represents the number of trials, and the y-axis lists the specific multiple-agent regimens.

outcomes were scored using a pre-defined scale (0, 0.5, 1, and 1.5; described in Methods) and listed in Supplementary Table S1. Zero scores indicate no efficacy or toxicity (failure); 0.5 indicates a positive response in a biomarker-selected population only; 1 indicates positive overall efficacy with no reported biomarker response; and 1.5 indicates both positive overall efficacy and a positive biomarker response. Table 2 presents the score distribution across PARPi and non-PARPi spaces. A comparison of PARP and non-PARP inhibitor trials (n=57 and n=32, respectively) reveals distinct outcome distributions. PARP inhibitor trials showed a higher proportion of failures (35.1% scoring 0) compared to non-PARP inhibitor trials (28.1% scoring 0). Conversely, non-PARP inhibitor trials exhibited a higher proportion of positive efficacy without a reported biomarker response (40.6% scoring 1) compared to PARP inhibitor trials (28.1% scoring 1). The proportion of trials showing both positive efficacy and a biomarker response (score 1.5) was relatively similar between the two classes (26.3% for PARP inhibitors and 25.0% for non-PARP inhibitors). PARP inhibitors also demonstrated a higher percentage of trials with positive biomarker response only (10.5% scoring 0.5) compared to non-PARP inhibitors (6.2%).

3.3 PARPis combinations: clinical trial outcomes with diverse DDAs

Of the initial 221 DDA-DDRi combination-arm trials, 127 in PARPi combination with DDAs and 57 had interpretable outcomes selected for further analysis and scored using pre-defined criteria (0, 0.5, 1, and 1.5, as described in methods). This analysis focused on eight PARPis, including five FDA approved drugs: olaparib (7), niraparib (8), rucaparib (9), talazoparib (10), and pamiparib (96) investigated in combination with DDAs (Supplementary Table S1, Figure 5). Supplementary Table S1 provides key highlights of these trials, including specific regimens, trial phases, overall outcomes, adverse effects, and the score`s distribution.

Among the FDA approved PARPi inhibitors, veliparib and olaparib are the most widely studied in combinations with DDAs (Figure 6A).

Multiple agents, including carboplatin with paclitaxel, demonstrated positive outcomes when tested in combination with three PARPis-olaparib, talazoparib, and veliparib (Figure 6A). Among the seven multiple-agent regimens combined with veliparib (as shown in Figure 6), six (85%) showed overall

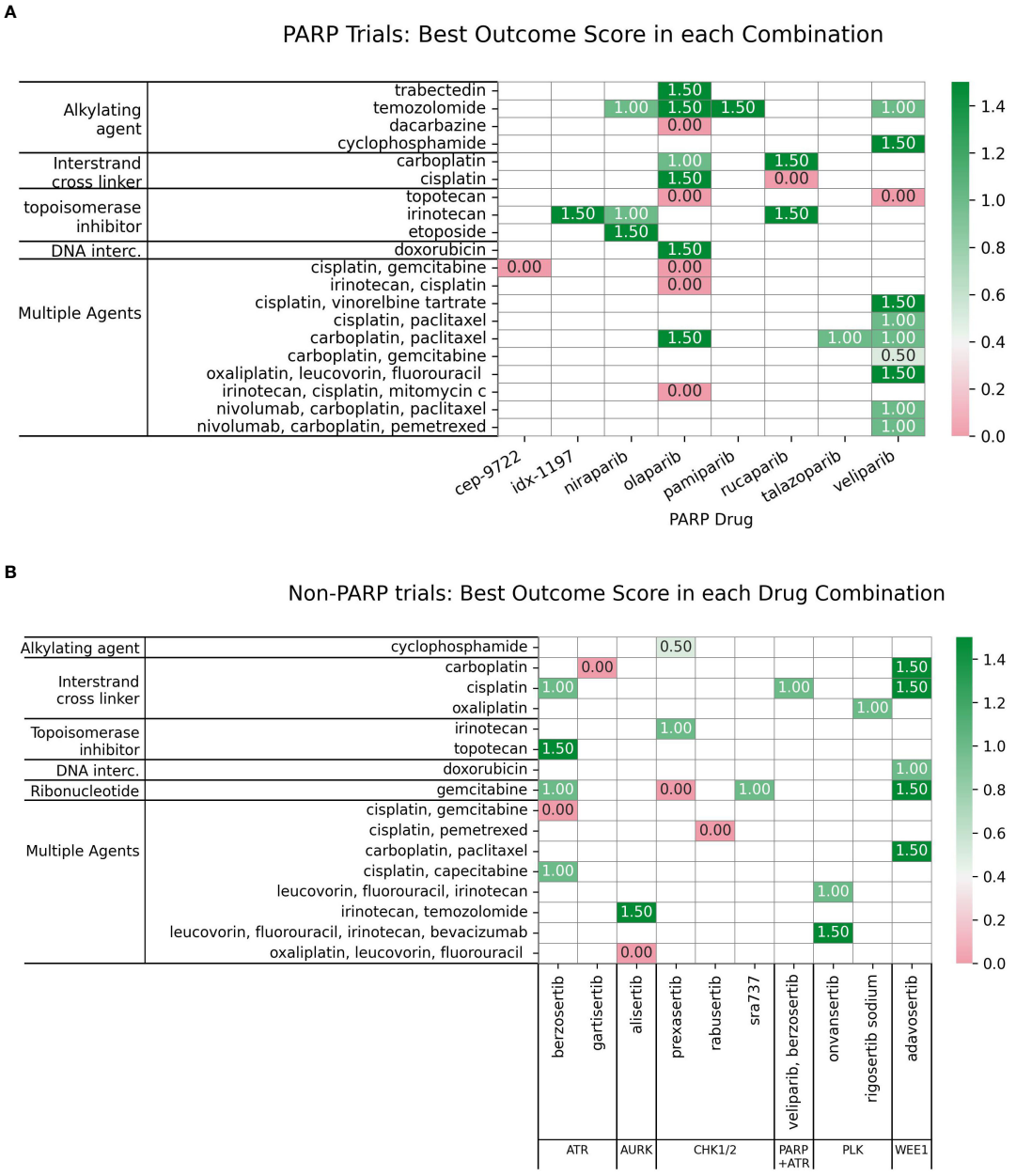

FIGURE 4
Number of trials distributed by clinical trial phase for each subclass of DDAs in combinations with **(A)** PARP inhibitors or **(B)** non-PARP DDR inhibitors. The x-axis represents the clinical trial phase, and the y-axis lists the number of combination-arm trials.

positive outcomes. Although the remaining regimen was not positive in the overall cohort, it did show efficacy in a biomarker-defined subpopulation. In trials investigating 22 PARPi-alkylating agent combinations and shown in Figure 6B, 45.5% (10 trials) showed no efficacy/toxicity (score 0). The remaining trials were evenly distributed across positive outcomes: 18.2% (4 trials each) demonstrated a biomarker-specific response (score 0.5), overall efficacy without biomarker information (score 1), and both overall efficacy and a positive biomarker response (score 1.5). This mixed outcome profile highlights the challenges and variability in achieving both efficacy and biomarker responses. While alkylating agents, particularly temozolomide (TMZ), showed promise in uterine leiomyosarcoma (uLMS) (31) and relapsed small cell lung carcinoma (SCLC) (97), not all combinations were successful (e.g., veliparib/cyclophosphamide in TNBC (98), and veliparib/TMZ in hepatocellular carcinoma (99). Dose-limiting toxicities, including myelosuppression, were also observed (100). Biomarker-driven approaches, such as ERCC1 expression in metastatic melanoma (101) and an 8-gene signature in sarcomas CDKN2A, PIK3R1, SLFN11, ATM, APEX2, BLM, XRCC2, MAD2L2 that may help predict better outcomes (102, 103), offer potential for tailoring therapies.

For PARPi-ICL combinations (n=6), the outcome distribution was: 3 trials (50%) scored 0, indicating failure/no efficacy/toxicity; 1

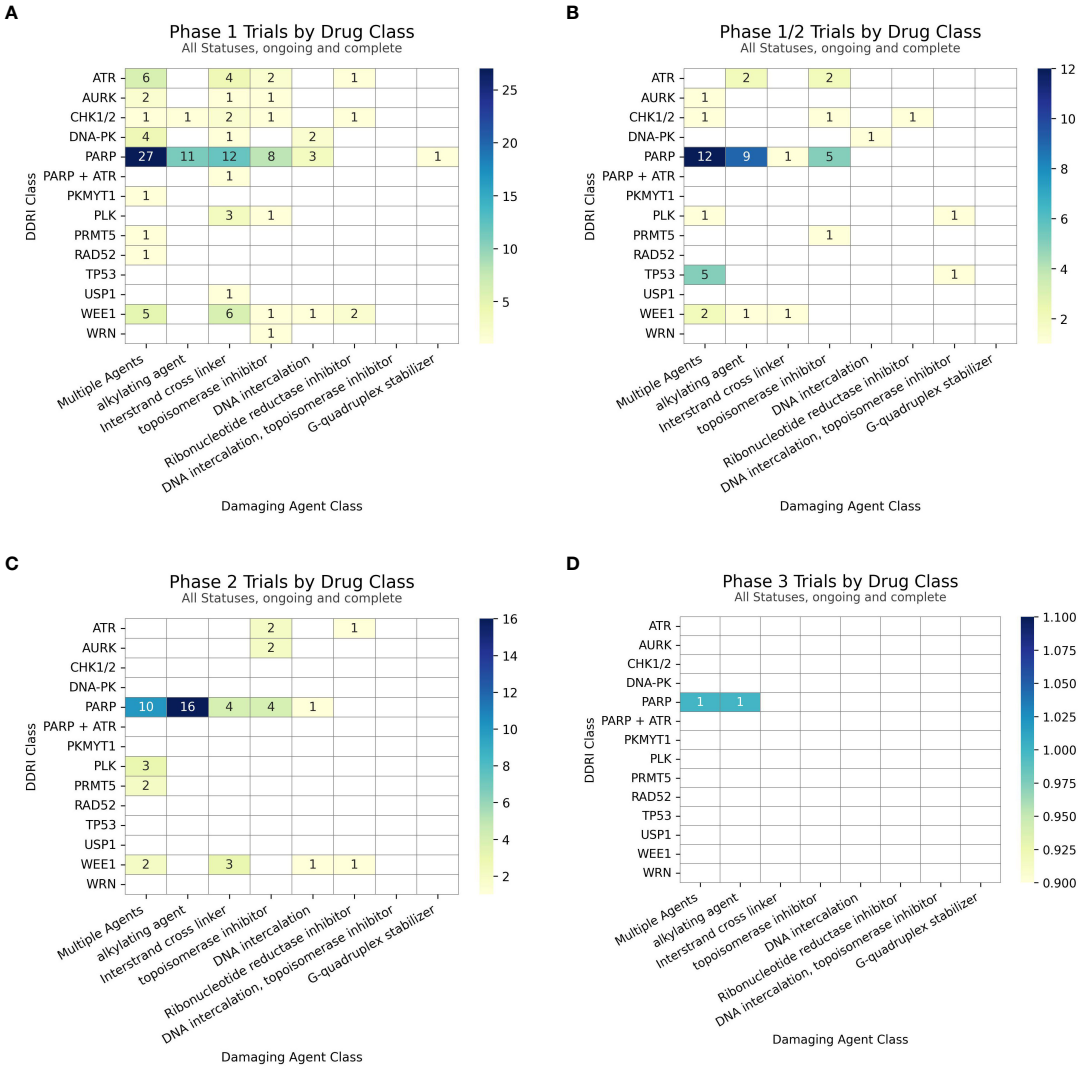

FIGURE 5
(A) Count of Phase 1 trial arms **(B)** Count of Phase 1/2 trial arms **(C)** Count of Phase 2 (inclusive of Phase 1/2) trial arms and **(D)** Count of Phase 3 trial arms with subtotals for combinations within each DDRi + DDA subclass.

TABLE 2 Distribution of scores across the PARP and non-PARP spaces.

DDRi Broad Class	Total number of trials	Number of trials by Outcome			
		Outcome Score			
		0	0.5	1.0	1.5
PARP Inhibitors	57	20	6	16	15
Non-PARP Inhibitors	32	9	2	13	8

The table summarizes the allocation of scores (0, 0.5, 1, and 1.5) for the outcomes of selected trials based on their classification within the PARP and non-PARP categories.

trial (16.7%) scored 1, reflecting positive overall efficacy without a reported biomarker response; and 2 trials (33.3%) scored 1.5, indicating both positive efficacy and a positive biomarker response (Figure 6B). Combinations of PARPi with ICL agents, such as platinum compounds, demonstrate synergy (104, 105), particularly in BRCA-mutated tumors, but overlapping myelotoxicity remains a significant challenge (Figure 7).

In contrast, PARPi-topoisomerase inhibitor combinations (n=6) showed a different profile: 2 trials (33.3%) scored 0; 1 trial (16.7%) scored 1; and 3 trials (50%) scored 1.5. This suggests a trend towards positive efficacy and biomarker responses, although failures were also observed (Figure 6B) Notably, BRCA mutation status has emerged as a key predictor of improved outcomes with these combinations. PARPi combinations with topoisomerase

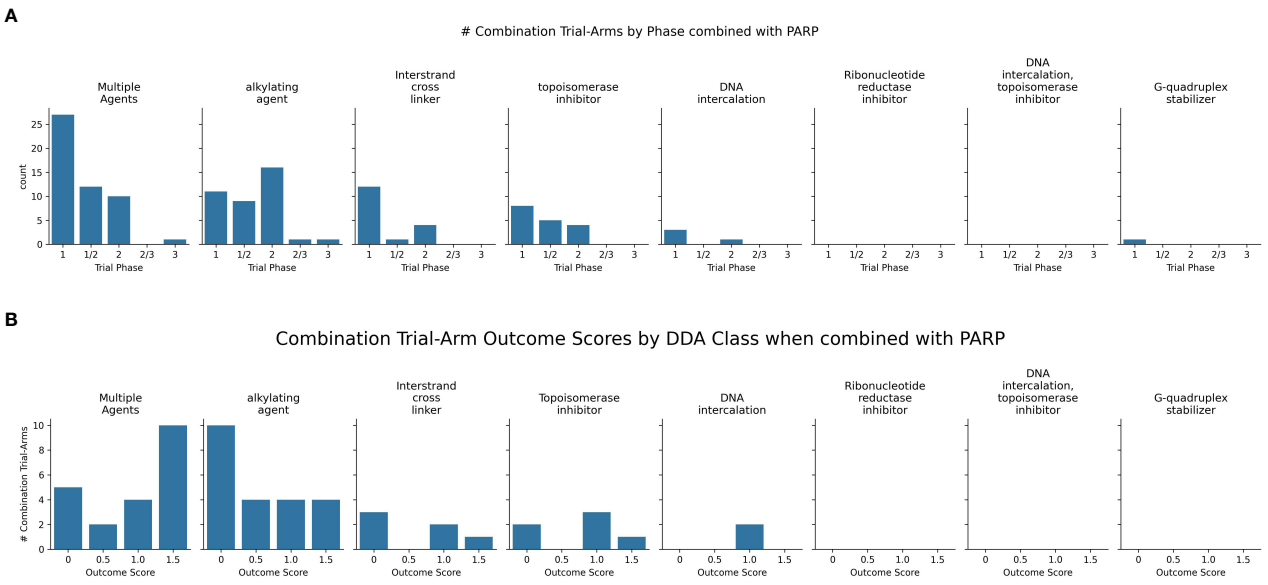

FIGURE 6
(A) Charts the highest combination trial-arm efficacy scores for PARPis combined with different DDA subclasses, illustrating which combinations have shown positive outcomes in at least one study. **(B)** Distribution of combination-arm trial's outcome scores by DDA subclasses for PARPis in combinations. The x-axis represents the specific outcome score, and the y-axis lists the number of combination-arm trials.

inhibitors (e.g., irinotecan, etoposide) have yielded mixed results, showing promise in some indications like platinum-resistant ovarian (106) and HRD-positive gastric cancers, especially with specific genetic mutations (107); however, significant hematological toxicities (108, 109) have also limited the development of certain combinations.

These results indicate distinct outcome profiles for different PARPi-DDA combinations. In contrast, PARPi-ICL combinations in this small sample show a mix of responses; PARPi-topoisomerase inhibitor combinations trend toward more positive efficacy and biomarker responses. PARPi-alkylating agent combinations show a more balanced distribution of positive and negative outcomes.

3.4 Non-PARPis combinations: clinical trial outcomes with diverse DDAs

Newer non-PARP DDRi targeting ATR, WEE1, and CHK1 also show promise in combination with DDAs (Supplementary Table S2, Figure 8).

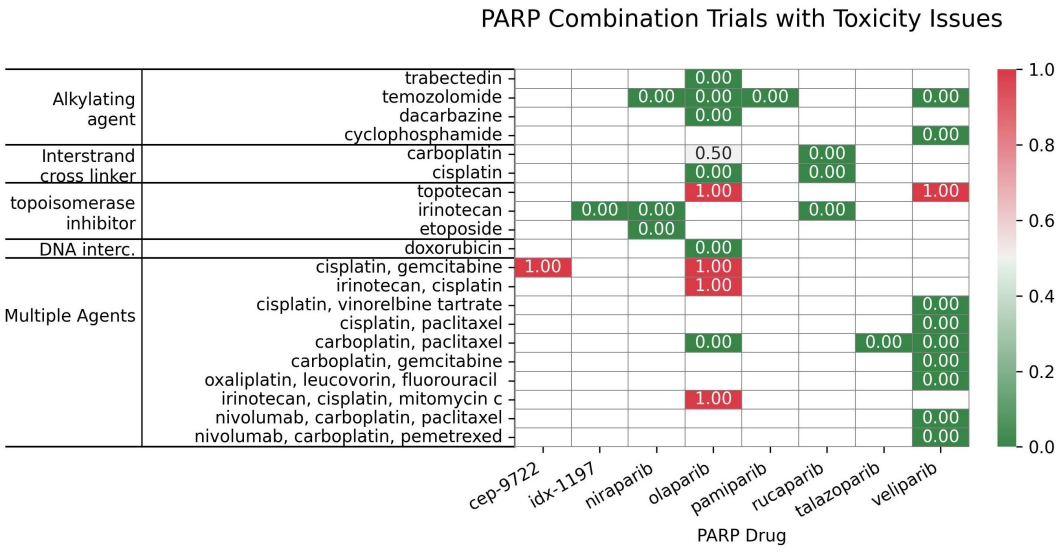

FIGURE 7
Distribution of the PARP inhibitors in combination with subclasses of DNA-damaging agents, categorized based on their toxicity scores.

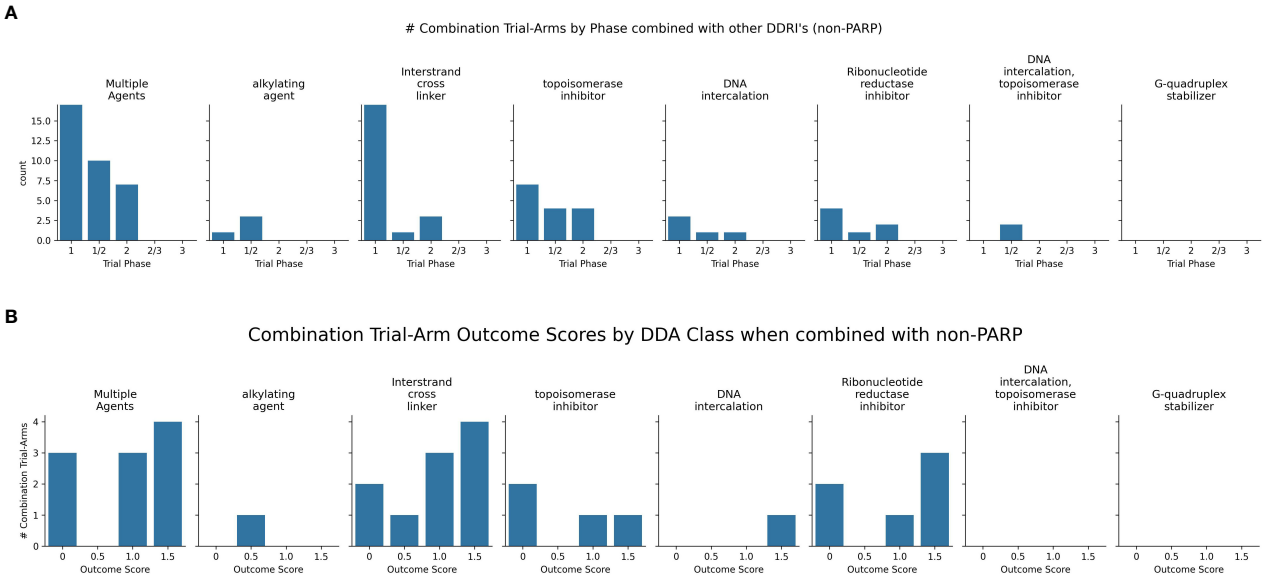

FIGURE 8
(A) Charts the highest combination trial-arm efficacy scores for non-PARPis combined with different DDA subclasses, illustrating which combinations have shown positive outcomes in at least one study. **(B)** Distribution of combination-arm trial's outcome scores by DDA subclasses for non-PARPis. The x-axis represents the specific outcome score, and the y-axis lists the number of combination-arm trials.

As shown in Figure 8B, non-PARPi combinations were evaluated more extensively with ICLs (n=10) than with alkylating agents (n=1). The one trial investigating alkylating agents combined with non-PARPis scored 0.5 (100%), indicating a positive biomarker response only. Among the ten ICL-NonPARPi combinations, 80% (8 trials) showed some level of positive outcome (scores 0.5, 1, or 1.5), with 40% (4 trials) demonstrating positive overall efficacy without biomarker information and 30% (3 trials) demonstrating both positive efficacy and a positive biomarker response. 20% (2 trials) showed no efficacy (score 0). For the four topoisomerase inhibitor combinations with non-PARPis, the distribution was: 2 trials (50%) scored 0; 1 trial (25%) scored 1; and one trial (25%) scored 1.5. These results suggest that ICL-NonPARPi combinations demonstrate a more varied response, with a mix of failures and positive efficacy outcomes. Topoisomerase-NonPARPi combinations show a mixed outcome profile, with 50% of trials showing no efficacy and 50% showing some positive outcome (score 1 or 1.5). Clinically, berzosertib (ATR inhibitor) has shown promise with topotecan in relapsed neuroendocrine cancers (110) and also improving outcomes with gemcitabine in platinum-resistant HGSOC (111) and Non-Small Cell Lung Cancer (NSCLC) with high TMB/LOH (112). The same trial showed a negative outcome score when used in combination with gemcitabine + cisplatin, which did not yield an established RP2D due to toxicity concerns (113). As revealed in Figure 8, WEE1 inhibitor adavosertib consistently achieved a score of 1.5 across 3 combination -arm trials when combined with ICL-inducing agents, demonstrating a potent synergistic interaction and suggesting a promising synthetic lethal strategy. Adavosertib demonstrated benefit in TP53-mutated patients with platinum agents or gemcitabine (114); specifically achieving a 43% overall response rate in platinum-resistant or refractory epithelial ovarian cancer when combined with carboplatin (115). Further details on these trials, including specific outcomes, can be found in Supplementary Table S2. These findings highlight the potential of non-PARP DDRis, mainly when combined with platinum-based chemotherapy and emphasize the importance of identifying genetic vulnerabilities like TP53 mutations.

4 Discussion

This analysis of DDRi combinations with DDAs reveals distinct outcome profiles depending on the specific DDRi class (PARP vs. non-PARP) and the DDA employed. While this review aimed to provide a comprehensive overview using a defined scoring system (0 for failure/no efficacy/toxicity to 1.5 for positive efficacy and biomarker response, as detailed in the Results section and summarized in Supplementary Tables S1, S2, Figures 6–8), the dynamic nature of this field and the focus on interpretable outcomes means that it may not be fully exhaustive of all published studies. Future research will provide additional insights.

For PARPi combinations, the outcome distribution varied considerably across DDA subclasses. In 22 PARPi-alkylating agent combination trials, a substantial proportion (45.5%, 10 trials) showed no efficacy/toxicity (score 0), highlighting a key challenge with this combination strategy. The remaining trials exhibited a more balanced distribution across positive outcomes, with similar proportions demonstrating a biomarker-specific response (score 0.5), overall efficacy without biomarker information (score 1), and combined efficacy and biomarker response (score 1.5), each at 18.2% (4 trials). This heterogeneity underscores the influence of tumor biology and emphasizes the need for careful patient selection. While specific

examples like olaparib/TMZ in uLMS (98) and SCLC (97) demonstrate promising efficacy, other combinations and tumor types did not show similar benefits, and dose-limiting toxicities were observed. This highlights the importance of biomarker-driven approaches, as exemplified by studies using ERCC1 expression (101) and 8-gene signatures (102, 103), to personalize treatment strategies.

In contrast, the limited data for PARPi-ICL combinations (n=6) revealed a distinct profile: (50%) showed no efficacy/toxicity (score 0), while 3 trials showed other positive outcome scores. This small sample size prevents definitive conclusions; however, it suggests that while synergy with platinum agents is theoretically sound (especially in BRCA-mutated tumors), clinical outcomes are not uniformly positive, and overlapping myelotoxicity remains a critical challenge. PARPi-topoisomerase inhibitor combinations (n=6) indicated a more promising trend, with a higher proportion of trials showing both positive efficacy and biomarker responses (50%, score 1.5), although failures were also observed (33.3%, score 0). This suggests that this combination strategy may be particularly promising in certain contexts, particularly in HRD-positive tumors. Furthermore, ongoing investigation of next-generation PARP1-selective inhibitors, e.g., NMS-03305293 (116) and AZD5305 (117), in combination with DDAs, aims to address toxicity and improve the therapeutic index.

Optimizing the delivery and tolerability of DNA-damaging agents can be a critical parallel strategy to enhancing their efficacy in combination with DDR inhibitors. Liposomal doxorubicin, for example, offers a more favorable pharmacokinetic profile and reduced cardiotoxicity, expanding its therapeutic window and making it a more suitable partner in regimens where cumulative cardiac risk is a limiting factor (118, 119). These advancements in formulation can help address the challenges of maximizing the therapeutic index of DNA-damaging agents for successful combination strategies with DDRis. In our analysis, all identified trials using doxorubicin in combination with DDRi employed a liposomal or pegylated liposomal formulation. Notably, the two PARP inhibitor trials—NCT03161132 (120, 121) and NCT00819221 (122)—demonstrated strong performance, receiving maximum scores of 1.5 for overall efficacy and biomarker relevance. Conventional doxorubicin was not studied in combination with DDRis. Nonetheless, these observations highlight the promise of novel formulation strategies to improve tolerability and expand the therapeutic potential of DDR-based combination therapies.

Non-PARPi combinations exhibited a different pattern. They were more extensively evaluated with ICLs (n=10) than alkylating agents (n=1), possibly reflecting a strategic focus on exploiting platinum-induced DNA damage. These ICL-NonPARPi combinations demonstrated promising activity, with the majority of trials (80%, 8 trials) showing some level of positive outcome. The distribution of these positive outcomes—40% (4 trials) demonstrating overall efficacy without biomarker information (score 1) and 30% (3 trials) demonstrating both efficacy and a positive biomarker response (score 1.5)—highlights the need for further investigation to understand the factors contributing to varied responses and to develop strategies for patient selection. The single trial evaluating alkylating-NonPARPi combinations prevents any meaningful conclusions. Topoisomerase-NonPARPi combinations (n=4) showed a mixed outcome profile, with 50% of trials showing no efficacy and 50% showing some positive outcome (score 1 or 1.5).

Comparing PARPi and non-PARP DDRi combinations, it is evident that different DDAs elicit distinct responses. While PARPi combinations show a more balanced distribution of outcomes across DDA subclasses (with the exception of the small ICL dataset), non-PARPi combinations appear to be more focused on ICLs, with a more varied range of responses. This highlights the importance of considering the specific DDR pathway targeted by the inhibitor and the type of DNA damage induced by the DDA when designing combination strategies. As the field evolves, refining these strategies and identifying new targets within the DDR network and combination agents is crucial. Advancing promising DDRi–DDA combinations will require further validation through large-scale clinical trials in well-defined patient populations, supported by the development of robust predictive biomarkers. Optimizing treatment sequencing and dosing will also be key to maximizing clinical benefits (2). Preclinical studies should continue elucidating synergistic mechanisms in diverse cancer models and investigating resistance mechanisms. Future research should focus on the rational selection of DDRi-DDA combinations based on tumor-specific DDR defects and explore multi-DDR targeting strategies to achieve deeper and more durable responses (123, 124). A data-driven approach with a higher level of automation could be highly beneficial for scientists and clinicians in determining and designing optimal combination trials.

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.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

RF: Conceptualization, Data curation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. NB: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. KB: Conceptualization, Supervision, Writing – review & editing. RE: Supervision, Writing –

review & editing. MC: Supervision, Writing – review & editing. PS: Funding acquisition, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. RF, NB, RE, MC, KB and PS have been salaried employees of or consultants to the pharmaceutical company Lantern Pharma Inc. ("Lantern"). MC and PS are officers of Lantern's subsidiary, Starlight Therapeutics Inc. The research reported on in this manuscript was funded by Lantern Pharma Inc. Employees, consultants and contractors of Lantern Pharma Inc. were involved in writing this article and in the design, collection, analysis, and interpretation of data reported on herein. The specific roles of these authors are articulated in the 'author contributions' section.

Conflict of interest

RF, NB, RE, MC, KB and PS have been salaried employees of or consultants to the pharmaceutical company Lantern Pharma Inc. ("Lantern"). MC and PS are officers of Lantern's subsidiary, Starlight Therapeutics Inc.

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.

This study received funding from Lantern Pharma Inc. Lantern Pharma Inc. was involved in the writing of this article, design, collection, analysis, and interpretation of data.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2025.1577468/full#supplementary-material

SUPPLEMENTARY TABLE 1
This table summarizes DDAs- PARPi combination-arm trials, including study ID, drugs, cancer types, phase, status, efficacy, biomarkers, toxicity-related discontinuations, adverse effects, treatment regimens, and trial dates/enrollment and scores, as defined in the method section. Abbreviations: partial response (PR), dose-limiting toxicity (DLT), recommended phase 2 dose (RP2D), stable disease (SD), objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), overall survival (mOS), adverse events (AEs), complete response (CR), duration of response (DoR), twice daily (BID), maximum tolerated dose (MTD), pharmacokinetics (PK), small-cell lung cancer (SCLC), triple-negative breast cancer (TNBC), non-small-cell lung cancer (NSCLC), glioblastoma (GBM), and pancreatic ductal adenocarcinoma (PDAC).

SUPPLEMENTARY TABLE 2
This table summarizes DDAs-NonPARPi combination-arm trials, including study ID, drugs, cancer types, phase, status, efficacy, biomarkers, toxicity-related discontinuations, adverse effects, treatment regimens, and trial dates/enrollment and scores, as defined in the method section. Abbreviations: partial response (PR), dose-limiting toxicity (DLT), recommended phase 2 dose (RP2D), stable disease (SD), objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), overall survival (mOS), adverse events (AEs), complete response (CR), duration of response (DoR), twice daily (BID), maximum tolerated dose (MTD), pharmacokinetics (PK), small-cell lung cancer (SCLC), non-small-cell lung cancer (NSCLC), primary platinum-resistant ovarian cancer (PROC), extrapulmonary small cell neuroendocrine carcinoma (EP-SCNC).

SUPPLEMENTARY TABLE 3
A list of combination-arm clinical trials without outcomes.

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