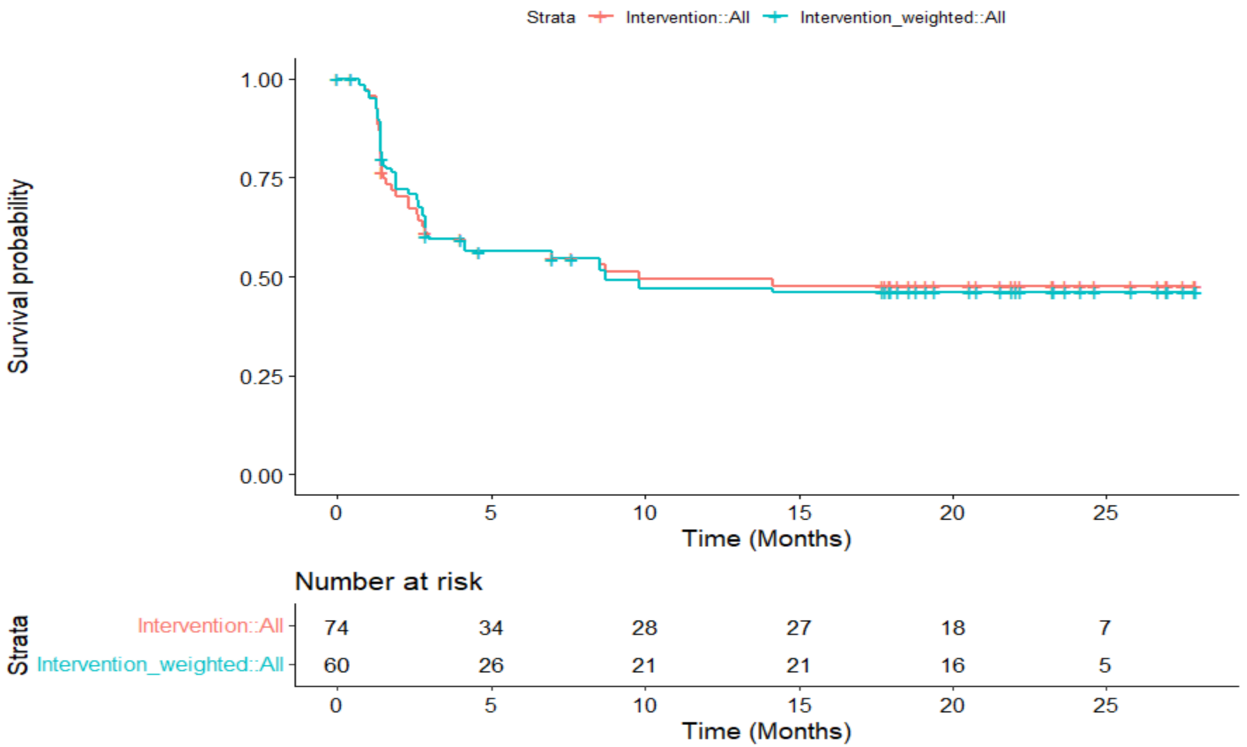
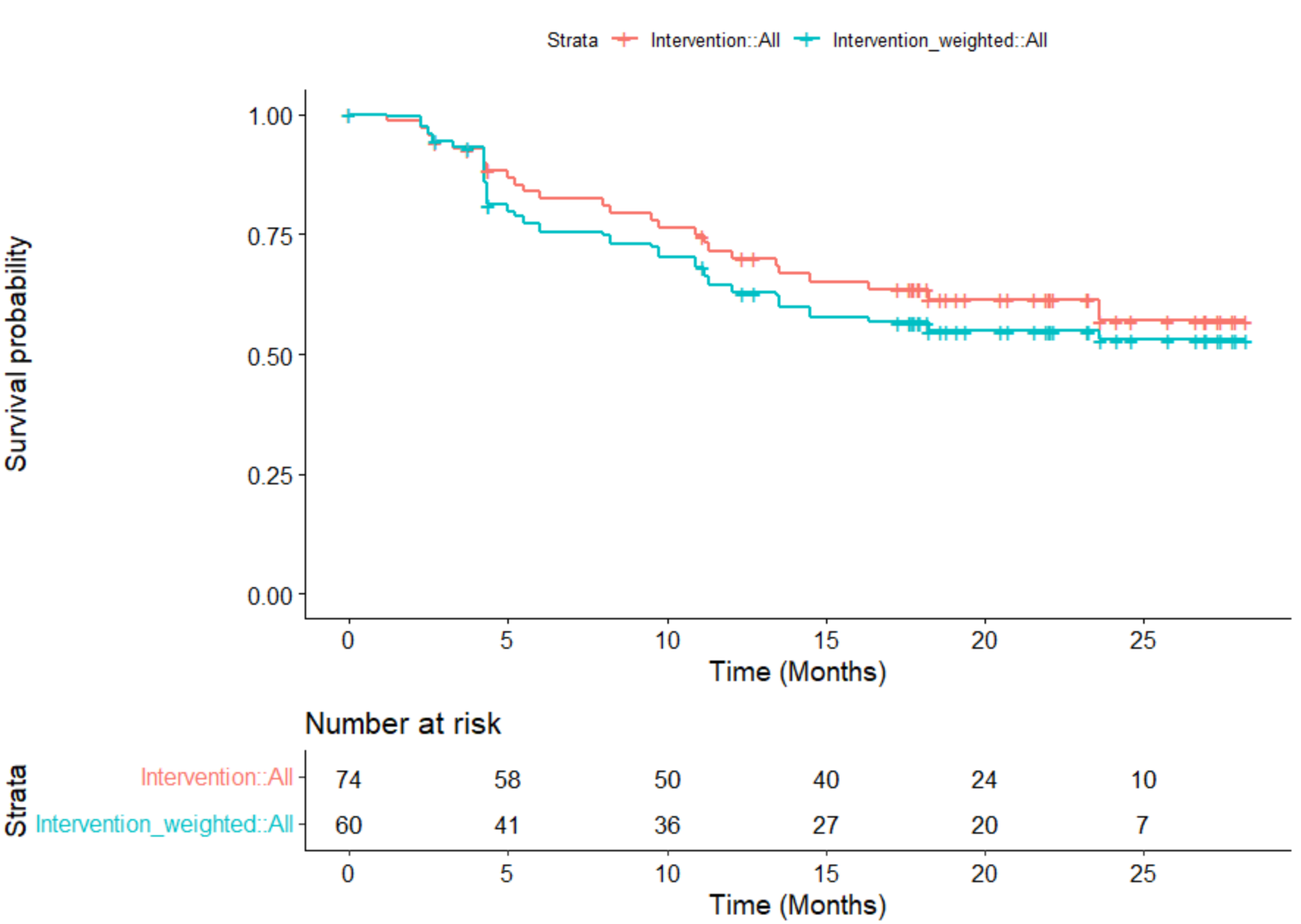
**Appendix**

**Appendix Table 1. Baseline characteristics of the ASTRUM-101 and CONCUR trial**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Original characteristics | | MAIC | |
| Serplulimab  (n=74) | Regorafenib  (n=136) | Serplulimab  (ESS=48.6) | Regorafenib  (n=136) |
| Age (years) |  |  |  |  |
| ＜65 | 86% | 70% | 70% | 70% |
| ≥65 | 14% | 30% | 30% | 30% |
| Sex |  |  |  |  |
| Men | 58% | 63% | 63% | 63% |
| Female | 42% | 38% | 38% | 38% |
| ECOG performance status |  |  |  |  |
| 0 | 47% | 26% | 26% | 26% |
| 1 | 53% | 74% | 74% | 74% |
| Histology |  |  |  |  |
| Adenocarcinoma | 96% | 96% | 96% | 96% |
| Mucinous carcinoma | 4% | 4% | 4% | 4% |
| Number of metastatic sites |  |  |  |  |
| Single | 26% | 21% | 21% | 21% |
| Multiple | 74% | 79% | 79% | 79% |
| Previous systemic anticancer treatment lines | | | | |
| 1-2 | 28% | 35% | 35% | 35% |
| ≥3 | 72% | 62% | 62% | 62% |
| Previous targeted biological treatment | | | | |
| None | 35% | 41% | 41% | 41% |
| Any | 65% | 59% | 59% | 59% |

ECOG: Eastern Cooperative Oncology Group

**a**

**b**

（a）presents original and weighted progression free survival curves of serplulimab. (b) presents original and weighted overall survival curves of serplulimab.

**Appendix Figure 1. Survival curves using matching-adjusted indirect comparison in serplulimab.**

**Appendix Table 2. AIC and BIC of 6 parametric distributions in serplulimab**

|  |  |  |
| --- | --- | --- |
|  | **AIC** | **BIC** |
| **PFS (standard model)** | | |
| Exponential | 221.25 | 223.55 |
| Gamma | 214.03 | 218.64 |
| **Gompertz** | **191.05** | **195.66** |
| Weibull | 211.24 | 215.85 |
| Log-Logistic | 205.70 | 210.30 |
| Log-Normal | 202.36 | 206.97 |
| **OS (mixture cure model)** | | |
| Exponential | 212.70 | 217.31 |
| Gamma | 207.83 | 214.74 |
| Gompertz | 212.22 | 219.13 |
| Weibull | 209.03 | 215.95 |
| Log-Logistic | 207.59 | 214.50 |
| **Log-Normal** | **206.43** | **213.35** |

AIC: Akaike information criterion, BIC: Bayesian information criterion, PFS: Progression free survival, OS: overall survival

**Appendix Table 3. AIC and BIC of 6 parametric distributions in regorafenib**

|  |  |  |
| --- | --- | --- |
|  | **AIC** | **BIC** |
| **PFS (standard model)** | | |
| Exponential | 605.32 | 608.23 |
| Gamma | 592.10 | 597.92 |
| Gompertz | 606.30 | 612.13 |
| Weibull | 597.87 | 603.69 |
| **Log-Logistic** | **580.52** | **586.35** |
| Log-Normal | 582.99 | 588.81 |
| **OS (standard model)** | | |
| Exponential | 743.71 | 746.62 |
| Gamma | 716.16 | 721.98 |
| Gompertz | 724.37 | 730.19 |
| Weibull | 716.88 | 722.71 |
| **Log-Logistic** | **723.86** | **683.31** |
| Log-Normal | 725.03 | 730.85 |

AIC: Akaike information criterion, BIC: Bayesian information criterion, PFS: Progression free survival, OS: overall survival

**Appendix Table 4. Diagnostic tests and costs**

|  |  |  |  |
| --- | --- | --- | --- |
| **Diagnostic test** | **Proportion of patients** | **Costs ($)** | **Source** |
| Physical examination | 100% | 4.55 | The proportion was derived from expert opinion and the cost was taken from 10 representative provinces or cities in China. |
| Laboratory testing |  |  |
| Blood routine | 100% | 2.32 |
| Urine routine | 100% | 1.06 |
| Stool routine | 100% | 0.85 |
| Fecal occult blood test | 100% | 0.89 |
| Biochemistry test | 100% | 42.43 |
| Biomarker test (CEA, AFP, CA199 and CA125) | 100% | 29.19 |
| Colonoscopy | 10% | 26.28 |
| Contrast CT scan (chest, abdomen and pelvis) | 5% | 149.43 |
| Contrast and non-contrast CT scan (abdomen and pelvis) | 5% | 179.69 |
| CT scan (chest) | 90% | 30.11 |
| PET-CT | 10% | 812.99 |
| MRI (pelvis) | 10% | 70.70 |
| Contrast MRI (liver) | 45% | 79.36 |
| Genetic test | 100% | 267.70 |

CEA: carcinoembryonic antigen, AFP: alpha fetoprotein, CT: computed tomography, CA 199: carbohydrate antigen 199, CA125: carbohydrate antigen 125, PET: positron emission tomography, MRI: magnetic resonance imaging

**Appendix Table 5. Patient monitoring information of patients treated by serplulimab and regorafenib**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion of patientsa** | **Frequency of visit per yeara** | | | | | | | | **Costsb**  **($)** |
| **the first 3 years in PFS** | | **4th-5th year in PFS** | | **After 5th year in PFS** | | **PD** | |
| Serplulimab | Regorafenib | Serplulimab | Regorafenib | Serplulimab | Regorafenib | Serplulimab | Regorafenib |
| Physical examination | 100% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 4.55 |
| Laboratory testing | | | | | | | | | | |
| Blood routine | 100% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 2.32 |
| Urine routine | 100% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 1.06 |
| Liver and kidney function | 100% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 24.40 |
| Biomarker test (CEA and CA199) | 100% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 17.39 |
| CT scan (Chest, abdomen and pelvis) | 100% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 120.45 |
| MRI (Chest, abdomen and pelvis) | 40% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 70.70 |
| PET-CT | 5.50% | 4 | 6 | 2 | 2 | 1 | 1 | 4 | 6 | 812.99 |

a Frequency of follow-up visit and the proportion of patients in each test was from expert opinion.

b Cost is the median price of each test in 10 representative provinces and cities.

CEA: carcinoembryonic antigen, CA 199: carbohydrate antigen 199, CT: computed tomography, MRI: magnetic resonance imaging, PET: positron emission tomography, PFS: Progression free survival, OS: overall survival

**Appendix Table 6. Subsequent treatment pattern for patients treated by serplulimab and regorafenib**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment pattern** | **Serplulimab** | **Regorafenib** | **Source** |
| Chemotherapy | 10% | 0% | Expert opinion |
| Chemotherapy+ targeted therapy | 10% | 0% |
| Targeted therapy | 40% | 0% |
| Immune checkpoint inhibitors | 0% | 75% |
| Radiotherapy | 15% | 0% |
| Clinical trial | 25% | 25% |

**Appendix Table 7. Subsequent treatment options and costs**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Subsequent therapy** | **Proportion of patients** | **Drug** | **Administration** | **Dosage** | **Unit cost ($)** | **Usage per unit** | **Costs of each treatment per cycle ($)** | **Cost of each pattern per cycle ($)** |
| **Chemotherapy** | | | | | | | | |
| Oxaliplatin | 16.67% | Oxaliplatin | 85mg/m2, iv drip, q2w | 50mg | 123.18 | 6.00 | 739.08 | 1,083.69 |
| Gemcitabine | 16.67% | Gemcitabine | 1000mg/m2, iv drip, once weekly for 3 weeks of each 28-day cycle | 200mg | 19.33 | 24.00 | 463.83 |
| Capecitabine | 8.33% | Capecitabine | 1250mg/m2, po, bid, day1-day14 of each 21-day cycle | 500mg | 17.24 | 12.44 | 214.50 |
| Vinorelbine Tartrate Capsules | 8.33% | VinorelbineTartrate Capsules | 10-40mg/d, po, qd, day1-day21 of each 28-day cycle | 20mg | 122.27 | 26.00 | 3,179.09 |
| Raltitrexed | 25.00% | Raltitrexed | 3mg/m2, iv drip, q3w | 2mg | 99.24 | 6.40 | 635.13 |
| Irinotecan | 16.67% | Irinotecan | 180mg/m2, iv drip, q2w | 40mg | 102.16 | 14.40 | 1,471.12 |
| Trifluridine-tipiracil | 8.33% | Trifluridine-tipiracil | 35mg/m2, po, qd, day1-5 and day8-12 of each 28-day cycle | 15mg | 631.41 | 3.73 | 2,357.25 |
| **Chemotherapy + targeted therapy** | | | | | | | | |
| Chemotherapy + Bevacizumab | 70% | Bevacizumab | 5mg/kg, iv drip, q2w | 100mg | 193.75 | 2.00 | 387.50 |  |
| Oxaliplatin | 85mg/m2, iv drip, q2w | 50mg | 123.18 | 6.00 | 739.08 | 1,902.98 |
| Calcium Levofolinate Hydrate | 400mg/m2, iv drip, q2w | 25mg | 7.03 | 52.00 | 365.62 |
| 5-Fluorouracil | 400mg/m2, iv, on day 1; 2400mg, iv drip on day 2, q2w | 250mg | 11.66 | 36.00 | 419.84 |
| Chemotherapy + Cetuximab | 30% | Cetuximab | 500mg/m2, iv, q2w | 100mg | 178.65 | 2.00 | 357.30 |
| Oxaliplatin | 85mg/m2, iv, q2w | 50mg | 123.18 | 6.00 | 739.08 |
| Calcium Levofolinate Hydrate | 400mg/m2, iv drip, q2w | 25mg | 7.03 | 52.00 | 365.62 |
| 5-Fluorouracil | 400mg/m2, iv, on day 1; 2400mg, iv drip on day 2, q2w | 250mg | 11.66 | 36.00 | 419.84 |
| **Targeted therapy** | | | | | | | | |
| Denosumab | 14.29% | Denosumab | 120mg, ih, q4w | 60mg | 243.99 | 1.00 | 243.99 | 1,083.92 |
| Regorafenib | 14.29% | Regorafenib | 160mg po, once daily on day1-21 of 28-day cycle | 40mg | 716.40 | 3.00 | 2,149.19 |
| Fruquintinib | 57.14% | Fruquintinib | 5mg, po, once daily on day1-21 of 28-day cycle | 5mg | 392.51 | 3.00 | 1,177.52 |
| Apatinib | 14.29% | Apatinib | 850mg, po, qd | 250mg | 161.41 | 3.00 | 484.22 |
| **Immune checkpoint inhibitors** | | | | | | | | |
| Camrelizumab | 28.57% | Camrelizumab | 3mg/kg, iv drip, q3w | 200mg | 434.34 | 1.33 | 579.12 | 2,399.62 |
| Pembrolizumab | 28.57% | Pembrolizumab | 200mg, iv drip, q3w | 100mg | 2,657.94 | 2.67 | 7087.85 |
| Toripalimab | 42.86% | Toripalimab | 3mg/kg, iv drip, q2w | 80mg | 121.95 | 4.00 | 487.80 |
| Tislelizumab | 0.00% | Tislelizumab | 200mg, iv drip, q3w | 100mg | 323.38 | 1.33 | 431.17 |
| Envafolimab | 0.00% | Envafolimab | 200mg, ih, q4w | 200mg | 887.07 | 1.00 | 887.07 |
| **Radiotherapy** | 100% | - | - | - | 116.46 | 1.00 | 116.46 | 116.46 |
| **Clinical trial** | 100% | - | - | - | 0.00 | 0.00 | 0.00 | 0.00 |

iv: intravenous infusion, po: by mouth, ih: hypodermic injection

q2w: every 2 weeks, q3w: every 3 weeks, q4w: every 4 weeks, qd: once daily, bid: twice a day

**Appendix Table 8. Model inputs**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Serplulimab** | | | **Regorafenib** | | |  |  |
| **Parameter** | **Base-case value** | **Range** | | **Base-case value** | **Range** | | **Distribution** | **Reference** |
| **Minimum** | **Maximum** | **Minimum** | **Maximum** |
| **Cost ($)** |  |  |  |  |  |  |  |  |
| Diagnosis | 519.26 | 415.41 | 623.11 | 519.26 | 415.41 | 623.11 | Gamma | Estimation\* |
| Drug acquisition costs per cycle | 3,315.68 |  |  | 2,149.19 |  |  | Gamma |  |
| Follow-up costs per cycle |  |  |  |  |  |  |  | Estimation\* |
| The first 3 years in PFS state | 75.65 | 60.52 | 90.78 | 113.48 | 90.78 | 136.17 | Gamma |  |
| The 4th-5th year in PFS state | 37.83 | 30.26 | 45.39 | 37.83 | 30.26 | 45.39 | Gamma |  |
| After 5th year in PFS state | 18.91 | 15.13 | 22.70 | 18.91 | 15.13 | 22.70 | Gamma |  |
| In PD state | 75.65 | 60.52 | 90.78 | 113.48 | 90.78 | 136.17 | Gamma |  |
| AE management costs |  |  |  |  |  |  |  | Estimation\* |
| Anemia | 6.96 | 5.57 | 8.35 | - |  |  | Gamma |  |
| Hyperbilirubinemia | 76.16 | 60.92 | 91.39 | 37.92 | 30.33 | 45.50 | Gamma |  |
| Impaired liver function | 76.16 | 60.92 | 91.39 | - |  |  | Gamma |  |
| Alanine aminotransferase elevated | 76.16 | 60.92 | 91.39 | 37.92 | 30.33 | 45.50 | Gamma |  |
| Aspartate aminotransferase elevated | - |  |  | 37.92 | 30.33 | 45.50 | Gamma |  |
| Lung infection | 88.85 | 71.08 | 106.62 | - |  |  | Gamma |  |
| Neutropenia | 62.62 | 50.10 | 75.15 | 84.93 | 67.94 | 101.91 | Gamma |  |
| Leukopenia | 62.62 | 50.10 | 75.15 | 26.48 | 21.18 | 31.77 | Gamma |  |
| Thrombocytopenia | - |  |  | 2,139.77 | 1,711.81 | 2,567.72 | Gamma |  |
| Diarrhea | 2.95 | 2.36 | 3.54 | 12.04 | 9.63 | 14.45 | Gamma |  |
| Creatine kinase elevated | 3.28 | 2.62 | 3.93 | - |  |  | Gamma |  |
| Hypertension | 0.18 | 0.14 | 0.21 | 0.18 | 0.14 | 0.21 | Gamma |  |
| Hand foot skin reaction | - |  |  | 16.18 | 12.94 | 19.42 | Gamma |  |
| Maculopapular rash | - | - | - | 17.63 | 14.11 | 21.16 | Gamma |  |
| Subsequent treatment costs per cycle | 749.71 | 599.76 | 899.65 | 1,799.71 | 1,439.77 | 2,159.66 | Gamma | Estimation\* |
| Hospitalization costs |  |  |  |  |  |  |  | Estimation\* |
| In PFS state | 73.38 | 58.71 | 88.06 | 0.00 | 0.00 | 0.00 | Gamma |  |
| In PD state | 110.08 | 88.06 | 132.09 | 146.77 | 117.41 | 176.12 | Gamma |  |
| Administration costs per cycle |  |  |  |  |  |  |  | Estimation\* |
| In PFS state | 2.97 | 2.37 | 3.56 | 0.00 | 0.00 | 0.00 | Gamma |  |
| In PD state | 1.67 | 1.34 | 2.00 | 1.80 | 1.44 | 2.16 | Gamma |  |
| End-of-life care costs | 2,046.84 | 1,637.47 | 2,456.21 | 2,046.84 | 1,637.47 | 2,456.21 | Gamma | [1] |
| **Utility values** |  |  |  |  |  |  |  |  |
| PFS | 0.84 | 0.672 | 1 | 0.84 | 0.672 | 1 | Beta | [2] |
| PD | 0.57 | 0.456 | 0.684 | 0.57 | 0.456 | 0.684 | Beta | [2] |
| **Disutility values** |  |  |  |  |  |  |  |  |
| Anemia | 0.085 | 0.068 | 0.102 | - |  |  | Beta | [3] |
| Hyperbilirubinemia | 0 | 0 | 0 | 0 | 0 | 0 | Beta | / |
| Impaired liver function | 0 | 0 | 0 | - |  |  | Beta | / |
| Alanine aminotransferase elevated | 0 | 0 | 0 | 0 | 0 | 0 | Beta | / |
| Aspartate aminotransferase elevated | - |  |  | 0 | 0 | 0 | Beta | / |
| Lung infection | 0.195 | 0.156 | 0.234 | - |  |  | Beta | [4] |
| Neutropenia | 0.0607 | 0.04856 | 0.07284 | 0.0607 | 0.04856 | 0.07284 | Beta | [3] |
| Leukopenia | 0.0607 | 0.04856 | 0.07284 | 0.0607 | 0.04856 | 0.07284 | Beta | [3] |
| Thrombocytopenia | - |  |  | 0.19 | 0.152 | 0.228 | Beta | [5] |
| Diarrhea | 0.07 | 0.056 | 0.084 | 0.07 | 0.056 | 0.084 | Beta | [5] |
| Creatine kinase elevated | 0 | 0 | 0 | - |  |  | Beta | / |
| Hypertension | 0.04 | 0.032 | 0.048 | 0.04 | 0.032 | 0.048 | Beta | [5] |
| Hand foot skin reaction | - |  |  | 0.116 | 0.0928 | 0.1392 | Beta | [6] |
| Maculopapular rash | - |  |  | 0.03248 | 0.025984 | 0.038976 | Beta | [3] |
| **Incidence of AEs (grade 3/4)** |  |  |  |  |  |  |  | ASTRUM-010 and [2] |
| Anemia | 10.81% | 8.65% | 12.97% | - |  |  | Beta |  |
| Hyperbilirubinemia | 6.76% | 5.41% | 8.11% | 6.00% | 4.80% | 7.20% | Beta |  |
| Impaired liver function | 5.41% | 4.33% | 6.49% | - |  |  | Beta |  |
| Alanine aminotransferase elevated | 1.35% | 1.08% | 1.62% | 7.00% | 5.60% | 8.40% | Beta |  |
| Aspartate aminotransferase elevated | - |  |  | 6.00% | 4.80% | 7.20% | Beta |  |
| Lung infection | 2.70% | 2.16% | 3.24% | - |  |  | Beta |  |
| Neutropenia | 4.05% | 3.24% | 4.86% | 2.00% | 1.60% | 2.40% | Beta |  |
| Leukopenia | 2.70% | 2.16% | 3.24% | 2.00% | 1.60% | 2.40% | Beta |  |
| Thrombocytopenia | - |  |  | 3.00% | 2.40% | 3.60% | Beta |  |
| Diarrhea | 2.70% | 2.16% | 3.24% | 1.00% | 0.80% | 1.20% | Beta |  |
| Creatine kinase elevated | 2.70% | 2.16% | 3.24% | - |  |  | Beta |  |
| Hypertension | 2.70% | 2.16% | 3.24% | 11.00% | 8.80% | 13.20% | Beta |  |
| Hand foot skin reaction | - |  |  | 16.00% | 12.80% | 19.20% | Beta |  |
| Maculopapular rash | - |  |  | 4.00% | 3.20% | 4.80% | Beta |  |

\*The estimated values were calculated based on expert opinion and prices form 10 representative provinces or cities in China. PFS: Progression free survival, PD: Progression disease, AE: adverse event

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