Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne  
on behalf of the RoB2 Development Group

**Version of 22 August 2019**

Completed risk of bias templates for the following study results:

**ATLANTIS\_PFS**

**ATLANTIS\_OS**

**ATLANTIS\_Response**

**ATLANTIS\_AEs**

**MEET-URO12\_PFS**

**MEET-URO12\_AEs**

**BAYOU\_AEs**

**BAYOU\_Response**

**BAYOU\_OS**

**BAYOU\_PFS**

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details ATLANTIS\_PFS**   |  |  | | --- | --- | | **Reference** | Crabb SJ, Hussain S, Soulis E, Hinsley S, Dempsey L, Trevethan A, Song Y, Barber J, Frew J, Gale J, Faust G, Brock S, McGovern U, Parikh O, Enting D, Sundar S, Ratnayake G, Lees K, Birtle AJ, Powles T, Jones RJ. **A Randomized, Double-Blind, Biomarker-Selected, Phase II Clinical Trial of Maintenance Poly ADP-Ribose Polymerase Inhibition With Rucaparib Following Chemotherapy for Metastatic Urothelial Carcinoma**. J Clin Oncol. 2023 Jan 1;41(1):54-64. doi: 10.1200/JCO.22.00405. Epub 2022 Aug 12. PMID: 35960902; PMCID: PMC9788980. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | rucaparib | Comparator: | placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Progression-free survival (PFS) |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “Median PFS was 35.3 weeks (80% CI, 11.7 to 35.6) with rucaparib  and 15.1 weeks (80% CI, 11.9 to 22.6) with placebo (hazard ratio, 0.53; 80% CI, 0.30 to 0.92; one-sided P 5 .07).” – abstract. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol  □ Statistical analysis plan (SAP)  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Patients were randomly assigned (1:1), on a double-blind basis, to treatment with rucaparib 600 mg twice a day orally, or matched placebo, to commence within 10 weeks of first-line chemotherapy. Random assignment was stratified via minimization factors (cisplatin-based v non–cisplatin-based first-line chemotherapy; Eastern Cooperative Oncology Group performance status 0 v 1 v 2; complete or partial response to first-line chemotherapy v stable disease; presence of visceral metastases; presence of measurable disease; and investigational site).” – p. 56.  “When the patient’s eligibility has been confirmed, and consent forms and randomisation forms have been completed, site staff must contact the Cancer Research UK Clinical Trials Unit, Glasgow to randomise the patient to the trial. Randomisation to the trial can be done by either telephone on the following numbers….” – p. 34 of protocol. | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Patient characteristics are presented in Table 1 and were reasonably balanced between allocated treatment arms.” – p. 57-58. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “… on a double-blind basis,” – p. 56 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “Analysis was conducted on an intention-to-treat (ITT) basis for all efficacy end points” – p. 56 | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Figure 1 CONSORT diagram indicates all 40 patients’ results were analyzed. Results are reported for all.  One patient allocated to rucaparib suffered cancer progression before  commencing treatment and did not receive rucaparib. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “disease progression as assessed by local investigators by RECIST version 1.1 … Disease evaluation was via cross-sectional imaging of the chest, abdomen, and pelvis at baseline, then every 12 weeks in year 1, every 16 weeks in year 2, and then every 24 weeks until disease progression. Patients were reviewed every 4 weeks until disease progression and then for survival status only.” | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | As above, all patients assessed by RECIST v 1.1 by local investigators. Study publication notes a lack of central radiology review but that this was partially mitigated by the double-blind design. | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | No, it was a double-blind study – local investigators were blinded. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4:** **Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | The analysis plan was specified in the protocol for the main study (ATLANTIS): “The primary end point is PFS. This has been chosen as it is largely objective and the majority of patients with UC display progression in accordance with RECIST 1.1 criteria.”  And, “Trial analysis plan” paragraph of ATLANTIS protocol  ATLANTIS protocol available via trials register: <https://www.isrctn.com/ISRCTN25859465> | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Only RECIST criteria used | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** | PFS was also assessed “within subgroups defined by the components of the DRD  biomarker.” which is reported as an exploratory post hoc analysis and is appropriate. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** | The study is judged to be at **low risk of bias for all domains** for this result. | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **ATLANTIS\_OS**   |  |  | | --- | --- | | **Reference** | Crabb SJ, Hussain S, Soulis E, Hinsley S, Dempsey L, Trevethan A, Song Y, Barber J, Frew J, Gale J, Faust G, Brock S, McGovern U, Parikh O, Enting D, Sundar S, Ratnayake G, Lees K, Birtle AJ, Powles T, Jones RJ. **A Randomized, Double-Blind, Biomarker-Selected, Phase II Clinical Trial of Maintenance Poly ADP-Ribose Polymerase Inhibition With Rucaparib Following Chemotherapy for Metastatic Urothelial Carcinoma**. J Clin Oncol. 2023 Jan 1;41(1):54-64. doi: 10.1200/JCO.22.00405. Epub 2022 Aug 12. PMID: 35960902; PMCID: PMC9788980. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | rucaparib | Comparator: | placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Overall survival (OS) |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “Median overall survival was not reached in the rucaparib treatment arm and 72.3 weeks (80% CI [51.7 to 85.4] for placebo with an adjusted HR of 1.22 [80% CI, 0.62 to 2.38]; P 5.35; unadjusted HR, 0.70 [80% CI, 0.4 to 1.2]; P 5 .21; Fig 3B)” – p.58 |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol  □ Statistical analysis plan (SAP)  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Patients were randomly assigned (1:1), on a double-blind basis, to treatment with rucaparib 600 mg twice a day orally, or matched placebo, to commence within 10 weeks of first-line chemotherapy. Random assignment was stratified via minimization factors (cisplatin-based v non–cisplatin-based first-line chemotherapy; Eastern Cooperative Oncology Group performance status 0 v 1 v 2; complete or partial response to first-line chemotherapy v stable disease; presence of visceral metastases; presence of measurable disease; and investigational site).” – p. 56.  “When the patient’s eligibility has been confirmed, and consent forms and randomisation forms have been completed, site staff must contact the Cancer Research UK Clinical Trials Unit, Glasgow to randomise the patient to the trial. Randomisation to the trial can be done by either telephone on the following numbers….” – p. 34 of protocol. | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Patient characteristics are presented in Table 1 and were reasonably balanced between allocated treatment arms.” – p. 57-58. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “… on a double-blind basis,” – p. 56 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “Analysis was conducted on an intention-to-treat (ITT) basis for all efficacy end points” – p. 56 | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Figure 1 CONSORT diagram indicates all 40 patients’ results were analyzed. Results are reported for all.  One patient allocated to rucaparib suffered cancer progression before  commencing treatment and did not receive rucaparib. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “overall survival (time from random assignment until death from any cause) – p.56 | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** |  | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | A double-blind study – local investigators were blinded. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | “The **OS** and PFS will be illustrated by using Kaplan–Meier plots.” – p. 5 (protocol/Fulton 2020). KM curves are reported in Fig 3, Crabb 2022. | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** |  | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** |  | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** | The study is judged to be at **low risk of bias for all domains** for this result. | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **ATLANTIS\_Response**   |  |  | | --- | --- | | **Reference** | Crabb SJ, Hussain S, Soulis E, Hinsley S, Dempsey L, Trevethan A, Song Y, Barber J, Frew J, Gale J, Faust G, Brock S, McGovern U, Parikh O, Enting D, Sundar S, Ratnayake G, Lees K, Birtle AJ, Powles T, Jones RJ. **A Randomized, Double-Blind, Biomarker-Selected, Phase II Clinical Trial of Maintenance Poly ADP-Ribose Polymerase Inhibition With Rucaparib Following Chemotherapy for Metastatic Urothelial Carcinoma**. J Clin Oncol. 2023 Jan 1;41(1):54-64. doi: 10.1200/JCO.22.00405. Epub 2022 Aug 12. PMID: 35960902; PMCID: PMC9788980. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | rucaparib | Comparator: | placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Response |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “A single further confirmed partial response occurred in one patient (5%) treated with rucaparib. No other objective radiologic responses to treatment occurred on the study, in either treatment group.” – p.59. See also Figure 5. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol  □ Statistical analysis plan (SAP)  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Patients were randomly assigned (1:1), on a double-blind basis, to treatment with rucaparib 600 mg twice a day orally, or matched placebo, to commence within 10 weeks of first-line chemotherapy. Random assignment was stratified via minimization factors (cisplatin-based v non–cisplatin-based first-line chemotherapy; Eastern Cooperative Oncology Group performance status 0 v 1 v 2; complete or partial response to first-line chemotherapy v stable disease; presence of visceral metastases; presence of measurable disease; and investigational site).” – p. 56.  “When the patient’s eligibility has been confirmed, and consent forms and randomisation forms have been completed, site staff must contact the Cancer Research UK Clinical Trials Unit, Glasgow to randomise the patient to the trial. Randomisation to the trial can be done by either telephone on the following numbers….” – p. 34 of protocol. | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Patient characteristics are presented in Table 1 and were reasonably balanced between allocated treatment arms.” – p. 57-58. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “… on a double-blind basis,” – p. 56 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “Analysis was conducted on an intention-to-treat (ITT) basis for all efficacy end points” – p. 56 | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Figure 1 CONSORT diagram indicates all 40 patients’ results were analyzed. Results are reported for all.  One patient allocated to rucaparib suffered cancer progression before  commencing treatment and did not receive rucaparib. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “disease progression as assessed by local investigators by RECIST version 1.1 … Disease evaluation was via cross-sectional imaging of the chest, abdomen, and pelvis at baseline, then every 12 weeks in year 1, every 16 weeks in year 2, and then every 24 weeks until disease progression. Patients were reviewed every 4 weeks until disease progression and then for survival status only.” – p. 56 | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | All patients assessed as noted above by local investigators. Study publication notes a lack of central radiology review but that this was partially mitigated by the double-blind design. | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Double-blind study – local investigators were blinded. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | “Response rates will be compared within subgroups in the context of a logistic model incorporating minimisation factors.” – p. 5 (protocol / Fulton 2020)  “A swimmer’s plot depicting time on treatment, response outcomes, and time to death is shown in Figure 5.” – p. 59 | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** |  | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** |  | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** | The study is judged to be at **low risk of bias for all domains** for this result. | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details ATLANTIS\_AEs**   |  |  | | --- | --- | | **Reference** | Crabb SJ, Hussain S, Soulis E, Hinsley S, Dempsey L, Trevethan A, Song Y, Barber J, Frew J, Gale J, Faust G, Brock S, McGovern U, Parikh O, Enting D, Sundar S, Ratnayake G, Lees K, Birtle AJ, Powles T, Jones RJ. **A Randomized, Double-Blind, Biomarker-Selected, Phase II Clinical Trial of Maintenance Poly ADP-Ribose Polymerase Inhibition With Rucaparib Following Chemotherapy for Metastatic Urothelial Carcinoma**. J Clin Oncol. 2023 Jan 1;41(1):54-64. doi: 10.1200/JCO.22.00405. Epub 2022 Aug 12. PMID: 35960902; PMCID: PMC9788980. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | rucaparib | Comparator: | placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Adverse events (AEs) |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “In the safety population (n=39) treatment-related adverse events were mostly low grade…Treatment-related adverse events (all grades) of fatigue (63.2% v 30.0%), nausea (36.8% v 5.0%), rash (21.1% v 0%), and raised alanine aminotransferase (57.9% v 10%) were more common with rucaparib.” – abstract.  See also p. 59 and Table 2. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol  □ Statistical analysis plan (SAP)  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Patients were randomly assigned (1:1), on a double-blind basis, to treatment with rucaparib 600 mg twice a day orally, or matched placebo, to commence within 10 weeks of first-line chemotherapy. Random assignment was stratified via minimization factors (cisplatin-based v non–cisplatin-based first-line chemotherapy; Eastern Cooperative Oncology Group performance status 0 v 1 v 2; complete or partial response to first-line chemotherapy v stable disease; presence of visceral metastases; presence of measurable disease; and investigational site).” – p. 56.  “When the patient’s eligibility has been confirmed, and consent forms and randomisation forms have been completed, site staff must contact the Cancer Research UK Clinical Trials Unit, Glasgow to randomise the patient to the trial. Randomisation to the trial can be done by either telephone on the following numbers….” – p. 34 of protocol. | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Patient characteristics are presented in Table 1 and were reasonably balanced between allocated treatment arms.” – p. 57-58. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “… on a double-blind basis,” – p. 56 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “The safety population comprised 39 patients (one patient allocated to rucaparib suffered cancer progression before commencing treatment).” – p. 59 | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Figure 1 CONSORT diagram indicates that one patient allocated to rucaparib suffered cancer progression before commencing treatment and did not receive rucaparib. Therefore the safety population was one less than the ITT population. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “safety, and tolerability (Common Terminology Criteria for Adverse Events, version 4.03).” – p.56 | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** |  | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Double-blind study – local investigators were blinded. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | “The worst toxicity grades experienced during chemotherapy will be compared by using the Mann–Whitney *U* test.” – p. 5 (protocol / Fulton 2020) | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Only CTCAE v. 4.03 used.  Worst toxicity grades, i.e. grade 3 and above are reported but not compared as intended, however there were not enough events at these grades to perform a statistical comparison. All grades of all AEs are reported with p-values. | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** |  | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** | The study is judged to be at **low risk of bias for all domains** for this result. | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **MEET-URO12\_PFS**   |  |  | | --- | --- | | **Reference** | Vignani F, Tambaro R, De Giorgi U, Giannatempo P, Bimbatti D, Carella C, Stellato M, Atzori F, Aieta M, Masini C, Hamzaj A, Ermacora P, Veccia A, Scandurra G, Gamba T, Ignazzi G, Pignata S, Di Napoli M, Lolli C, Procopio G, Pierantoni F, Zonno A, Santini D, Di Maio M; Meet-URO12 Investigators. **Addition of Niraparib to Best Supportive Care as Maintenance Treatment in Patients with Advanced Urothelial Carcinoma Whose Disease Did Not Progress After First-line Platinum-based Chemotherapy: The Meet-URO12 Randomized Phase 2 Trial**. Eur Urol. 2023 Jan;83(1):82-89. doi: 10.1016/j.eururo.2022.09.025. Epub 2022 Oct 8. PMID: 36216658. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | Niraparib plus best supportive care | Comparator: | Best supportive care alone |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Progression-free survival (PFS) |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “The median PFS was 2.1 mo in arm A and 2.4 mo in arm B (hazard ratio 0.92; 95% confidence interval 0.49–1.75, p = 0.81). The 6-mo progression-free rates were 28.2% and 26.3%, respectively.” – abstract. See also p. 85-86 and Figure 2. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol – journal article supplement 3  □ Statistical analysis plan (SAP)  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |
|  |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Randomization was performed centrally, through a dedicated web platform (www.meet-uro12.it), by a computer-driven minimization procedure. The type of response to first-line chemotherapy (OR vs SD) and ECOG PS (0 vs 1) were stratification variables. There was no blinding procedure for patients and physicians.” - p. 84. | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Baseline characteristics of the patients are reported in Table 1.” – p. 84.  Proportionally more patients had lymph node only involvement in the BSC arm which could give them a more favourable prognosis than the niraparib arm. However, any additional benefit may be offset by the higher proportion of patients (9%) in the BSC arm with visceral disease, which is associated with poor prognosis.  Proportionally more patients received cisplatin as the previous platinum agent in the niraparib arm whereas proportionally more patients received carboplatin as the previous platinum agent in the BSC arm. This could imply a fitter group of patients in the niraparib arm (as cisplatin is a more challenging chemotherapy) and, in turn, may over-estimate the efficacy and safety of niraparib in this study. However, the objective response to previous chemotherapy was similar between arms – most likely as a result of the stratification process noted above. Furthermore, the results of the Meet-URO12 study did not show a significant survival benefit for niraparib versus BSC. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | Due to the small sample size, the imbalance in baseline characteristics is not necessarily significant, and has not been tested for statistical significance, however the differences are not judged to be clinically significant, as noted in 1.3. | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | Open-label trial. | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “All the efficacy analyses were performed on an intention-to-treat (ITT) basis. PFS was defined as the time between randomization and progression  or death (whichever occurred first) or the last assessment for patients  alive without progression. Patients who discontinued treatment due to  symptomatic deterioration even in the absence of radiological progression  were considered progressive at the date of symptomatic deterioration.” – p. 84. | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Yes – see CONSORT diagram in Figure 1 | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “ Progression will be assessed following RECIST criteria ( v.1.1 ), using investigator's review. ” – protocol.  PFS was planned to be measured after 65 events, however as the study had to be stopped due to ethical reasons it was measured after 47 events. This is appropriate and affects the strength of the results (power) not risk of bias. | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** |  | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** |  | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** | Use of RECIST is objective and does not involve judgement. | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Data was unblinded throughout as an open-label study. Recruitment to the trial stopped for ethical reasons because the standard of care changed for the comparator arm. “Consequently, we amended the study protocol to perform an analysis with lower statistical power. A PFS analysis was performed after 47 events, which allow a power of around 70% to detect the originally hypothesized 3-mo improvement in the median PFS.” – p.87. | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Only used RECIST 1.1 | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** | PFS at 6 months was a separate prespecified secondary endpoint. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** | Mainly due to the open-label nature of the trial, and that proportionally more patients in the experimental arm had had previous therapy with cisplatin and may be a fitter population. | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **MEET-URO12\_AEs**   |  |  | | --- | --- | | **Reference** | Vignani F, Tambaro R, De Giorgi U, Giannatempo P, Bimbatti D, Carella C, Stellato M, Atzori F, Aieta M, Masini C, Hamzaj A, Ermacora P, Veccia A, Scandurra G, Gamba T, Ignazzi G, Pignata S, Di Napoli M, Lolli C, Procopio G, Pierantoni F, Zonno A, Santini D, Di Maio M; Meet-URO12 Investigators. **Addition of Niraparib to Best Supportive Care as Maintenance Treatment in Patients with Advanced Urothelial Carcinoma Whose Disease Did Not Progress After First-line Platinum-based Chemotherapy: The Meet-URO12 Randomized Phase 2 Trial**. Eur Urol. 2023 Jan;83(1):82-89. doi: 10.1016/j.eururo.2022.09.025. Epub 2022 Oct 8. PMID: 36216658. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | Niraparib plus best supportive care | Comparator: | Best supportive care alone |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Adverse events |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “The most common adverse events with niraparib were anemia (50%,grade [G]3 11%), thrombocytopenia (37%, G3–4 16%), neutropenia (21%, G3 5%), fatigue (32%, G3 16%), constipation (32%, G3 3%), mucositis (13%, G3 3%), and nausea (13%, G3 3%).” – abstract. See also p. 86 and Table 2. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol – journal article supplement 3  □ Statistical analysis plan (SAP)  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Randomization was performed centrally, through a dedicated web platform (www.meet-uro12.it), by a computer-driven minimization procedure. The type of response to first-line chemotherapy (OR vs SD) and ECOG PS (0 vs 1) were stratification variables. There was no blinding procedure for patients and physicians.” – p. 84. | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Baseline characteristics of the patients are reported in Table 1.” – p. 84.  Proportionally more patients had lymph node only involvement in the BSC arm which could give them a more favourable prognosis than the niraparib arm. However, any additional benefit may be offset by the higher proportion of patients (9%) in the BSC arm with visceral disease, which is associated with poor prognosis.  Proportionally more patients received cisplatin as the previous platinum agent in the niraparib arm whereas proportionally more patients received carboplatin as the previous platinum agent in the BSC arm. This could imply a fitter group of patients in the niraparib arm (as cisplatin is a more challenging chemotherapy) and, in turn, may over-estimate the efficacy and safety of niraparib in this study. However, the objective response to previous chemotherapy was similar between arms – most likely as a result of the stratification process noted above. Furthermore, the results of the Meet-URO12 study did not show a significant survival benefit for niraparib versus BSC. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | Due to the small sample size, the imbalance in baseline characteristics is not necessarily significant, and has not been tested for statistical significance, however the differences are not judged to be clinically significant, as noted in 1.3. | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | Open-label trial. | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “All patients who received at least one dose of treatment were eligible  for a safety analysis.” – p. 84. | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | Yes – see CONSORT diagram in Figure 1  Only one patient did not receive niraparib in the interventional arm, and therefore was not available for analysis of adverse events. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | Protocol states that the definitions of adverse events and grading of severity is according to CTCAE v4.03 | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | Use of common terminology and grading – CTCAE. | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | AEs were assessed by the Investigator at each institution. Investigators were unblinded – open-label study. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** | Use of CTCAE limits assessors’ subjective judgement | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Although the protocol was amended to take into account the availability of avelumab it did not have any implications for adverse events because the only changes made were to the sample size and no changes appear to have been made for the actual outcome measures. | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Only CTCAE terminology and grading used. | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** |  | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | The change to the analysis plan due to the availability of avelumab involved a reduction in the power calculation which reduces the certainty of results but does not introduce risk of bias. | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **BAYOU\_AEs**   |  |  | | --- | --- | | **Reference** | Rosenberg JE, Park SH, Kozlov V, Dao TV, Castellano D, Li JR, Mukherjee SD, Howells K, Dry H, Lanasa MC, Stewart R, Bajorin DF. **Durvalumab Plus Olaparib in Previously Untreated, Platinum-Ineligible Patients With Metastatic Urothelial Carcinoma: A Multicenter, Randomized, Phase II Trial (BAYOU)**. J Clin Oncol. 2023 Jan 1;41(1):43-53. doi: 10.1200/JCO.22.00205. Epub 2022 Jun 23. PMID: 35737919; PMCID: PMC9788981. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | Durvalumab plus olaparib | Comparator: | Durvalumab plus placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Adverse events (AEs) |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “Treatment-related grade 3 or 4 adverse events occurred in 18% and 9% of patients, respectively.” – abstract. See also p. 49 and Table 3. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol – available from clinicaltrials.gov  X□ Statistical analysis plan (SAP) – available from clinicaltrials.gov  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Random assignment was done using an interactive voice/web response system.” – p. 44 | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Baseline characteristics were generally well balanced between treatment  groups (Table 1).” – p. 46. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “The BAYOU study is a randomized, multicenter, **doubleblind**, phase II trial designed to evaluate the efficacy and safety of durvalumab plus olaparib versus durvalumab **plus placebo**” – p. 44 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “Safety and tolerability were assessed in all treated patients.” – p. 46. | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | CONSORT diagram (Figure 1) shows 76/78 patients received durvalumab plus Olaparib, and 76/76 patients received durvalumab plus placebo. Numbers discontinuing treatment are similar between treatment arms, the intervention arm experienced one protocol violation. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “Adverse events (AEs) were monitored throughout the treatment period and up to 90 days after the last dose of study drug. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.” – p. 45. | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** |  | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Study was double-blind. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Protocol dated July 2021; AE reporting in study publication matches the protocol (9.4.3). | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Only CTCAE used. | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** |  | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **BAYOU\_Response**   |  |  | | --- | --- | | **Reference** | Rosenberg JE, Park SH, Kozlov V, Dao TV, Castellano D, Li JR, Mukherjee SD, Howells K, Dry H, Lanasa MC, Stewart R, Bajorin DF. **Durvalumab Plus Olaparib in Previously Untreated, Platinum-Ineligible Patients With Metastatic Urothelial Carcinoma: A Multicenter, Randomized, Phase II Trial (BAYOU)**. J Clin Oncol. 2023 Jan 1;41(1):43-53. doi: 10.1200/JCO.22.00205. Epub 2022 Jun 23. PMID: 35737919; PMCID: PMC9788981. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | Durvalumab plus olaparib | Comparator: | Durvalumab plus placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Response |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “objective responses occurred in 22 patients (28.2%) in the durvalumab plus Olaparib group and in 14 patients (18.4%) in the durvalumab plus placebo group (odds ratio, 1.76; 95% CI, 0.82 to 3.78)” – p. 49. See also Table 2. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol – available from clinicaltrials.gov  X□ Statistical analysis plan (SAP) – available from clinicaltrials.gov  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Random assignment was done using an interactive voice/web response system.” – p. 44 | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Baseline characteristics were generally well balanced between treatment  groups (Table 1).” – p. 46. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “The BAYOU study is a randomized, multicenter, **doubleblind**, phase II trial designed to evaluate the efficacy and safety of durvalumab plus olaparib versus durvalumab **plus placebo**” – p. 44 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | ITT analysis and pre-specified subgroup analysis for patients with HRR mutation status. | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | CONSORT diagram (Figure 1) shows 76/78 patients received durvalumab plus Olaparib, and 76/76 patients received durvalumab plus placebo. Numbers discontinuing treatment are similar between treatment arms, the intervention arm experienced one protocol violation. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “…assessed by investigators according to RECIST v1.1)” – p. 45.  “ Radiologic efficacy was assessed from images collected every 8 weeks for the first 48 weeks after random assignment and every 12 weeks thereafter until RECIST v1.1-defined disease progression. Assessments of tumor response were confirmed no less than 4 weeks and no more than 8 weeks after the prior assessment.” – p. 45. | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** |  | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Study was double-blind. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Protocol dated July 2021 and PFS analyses reported (statistical analysis paragraph and results) match that in the protocol (9.4.2.). | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Only RECIST 1.1 measure was used. | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** | Analyses for HRR status subgroup was prespecified in the protocol (9.4.2.4) and reported in the study publication (p. 49 and Table 2). | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne  
on behalf of the RoB2 Development Group

**Version of 22 August 2019**

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **BAYOU\_OS**   |  |  | | --- | --- | | **Reference** | Rosenberg JE, Park SH, Kozlov V, Dao TV, Castellano D, Li JR, Mukherjee SD, Howells K, Dry H, Lanasa MC, Stewart R, Bajorin DF. **Durvalumab Plus Olaparib in Previously Untreated, Platinum-Ineligible Patients With Metastatic Urothelial Carcinoma: A Multicenter, Randomized, Phase II Trial (BAYOU)**. J Clin Oncol. 2023 Jan 1;41(1):43-53. doi: 10.1200/JCO.22.00205. Epub 2022 Jun 23. PMID: 35737919; PMCID: PMC9788981. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | Durvalumab plus olaparib | Comparator: | Durvalumab plus placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Overall survival (OS) |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “Median overall survival was 10.2 months (95% CI, 7.0 to 13.9) and 10.7 months (95% CI, 7.2 to 17.3), respectively (HR, 1.07; 95% CI, 0.72 to 1.61).” - abstract |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol – available from clinicaltrials.gov  X□ Statistical analysis plan (SAP) – available from clinicaltrials.gov  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Random assignment was done using an interactive voice/web response system.” – p. 44 | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Baseline characteristics were generally well balanced between treatment  groups (Table 1).” – p. 46. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “The BAYOU study is a randomized, multicenter, **doubleblind**, phase II trial designed to evaluate the efficacy and safety of durvalumab plus olaparib versus durvalumab **plus placebo**” – p. 44 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “Secondary end points included OS in the ITT population…” – p. 45.  “In both the ITT population and in patients with HRRm [pre-specified subgroup], other secondary end points (as assessed by investigators according to RECIST v1.1) included … the proportion of patients alive and progression free at 6 months” – p. 45. | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | CONSORT diagram (Figure 1) shows 76/78 patients received durvalumab plus Olaparib, and 76/76 patients received durvalumab plus placebo. Numbers discontinuing treatment are similar between treatment arms, the intervention arm experienced one protocol violation. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “Survival was assessed every 2 months after treatment discontinuation. – p. 45 | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** |  | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Study was double-blind. No information about blinding at the central laboratory which was probably only used to assess tumour samples for HRR mutation status. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Protocol dated July 2021; and OS analyses reported in the study publication (statistical analysis paragraph and results p. 49) match that in the protocol (9.4.2.2). | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** |  | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** | Subgroup analyses were prespecified in the protocol if there were sufficient OS events (9.4.2.2) and reported in the study publication for the HRR subgroup (p. 49). | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne  
on behalf of the RoB2 Development Group

**Version of 22 August 2019**

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details** **BAYOU\_PFS**   |  |  | | --- | --- | | **Reference** | Rosenberg JE, Park SH, Kozlov V, Dao TV, Castellano D, Li JR, Mukherjee SD, Howells K, Dry H, Lanasa MC, Stewart R, Bajorin DF. **Durvalumab Plus Olaparib in Previously Untreated, Platinum-Ineligible Patients With Metastatic Urothelial Carcinoma: A Multicenter, Randomized, Phase II Trial (BAYOU)**. J Clin Oncol. 2023 Jan 1;41(1):43-53. doi: 10.1200/JCO.22.00205. Epub 2022 Jun 23. PMID: 35737919; PMCID: PMC9788981. |   **Study design**   |  |  | | --- | --- | | X | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | □ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | Durvalumab plus olaparib | Comparator: | Durvalumab plus placebo |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Progression-free survival (PFS) |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | “median PFS was 4.2 months (95% CI, 3.6 to 5.6) for durvalumab plus olaparib and 3.5 months (95% CI, 1.9 to 5.1) for durvalumab plus placebo (hazard ratio [HR], 0.94; 95% CI, 0.64 to 1.39; log-rank P value, .789)” - abstract |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | X□ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  X□ Journal article(s) with results of the trial  X□ Trial protocol – available from clinicaltrials.gov  X□ Statistical analysis plan (SAP) – available from clinicaltrials.gov  □ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1: Risk of bias arising from the randomization process**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Random assignment was done using an interactive voice/web response system.” – p. 44 | Y / PY / PN / N / NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y / PY / PN / N / NI |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | “Baseline characteristics were generally well balanced between treatment  groups (Table 1).” – p. 46. Reviewer agrees. | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during the trial?** | “The BAYOU study is a randomized, multicenter, **doubleblind**, phase II trial designed to evaluate the efficacy and safety of durvalumab plus olaparib versus durvalumab **plus placebo**” – p. 44 | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | Y / PY / PN / N / NI |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | “investigator-assessed progression-free survival (PFS; according to RECIST v1.1) in the intention-to-treat (ITT) population, which included all randomly assigned patients.” – p. 45  “Primary analysis of PFS was performed at one time point, when approximately 118 PFS events had occurred (79% maturity) … across both treatment groups” – p. 46 | Y / PY / PN / N / NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 3: Missing outcome data

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | CONSORT diagram (Figure 1) shows 76/78 patients received durvalumab plus Olaparib, and 76/76 patients received durvalumab plus placebo. Numbers discontinuing treatment are similar between treatment arms, the intervention arm experienced one protocol violation. | Y / PY / PN / N / NI |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 4: Risk of bias in measurement of the outcome

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | “investigator-assessed progression-free survival (PFS; according to RECIST v1.1)”; “Radiologic efficacy was assessed from images collected every 8 weeks for the first 48 weeks after random assignment and every 12 weeks thereafter until RECIST v1.1-defined disease progression.” | Y / PY / PN / N / NI |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | “Tumor samples were assessed for HRR mutation status at a central laboratory” | Y / PY / PN / N / NI |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Study was double-blind. No information about blinding at the central laboratory. | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Domain 5: Risk of bias in selection of the reported result

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | Protocol dated July 2021 and PFS analyses reported (statistical analysis paragraph and results) match that in the protocol (9.4.2.1). | Y / PY / PN / N / NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Only RECIST 1.1 was used to measure PFS | Y / PY / PN / N / NI |
| **5.3 ... multiple eligible analyses of the data?** | Analyses for HRR status and Bajorin risk factor subgroups were prespecified in the protocol (9.4.2.1) and reported in the paper (p. 49) | Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

|  |  |  |
| --- | --- | --- |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).