Supplementary Table 1

Biomarker characteristics of included studies

|  |  |  |  |
| --- | --- | --- | --- |
|  | ATLANTIS [1] | Meet-URO12 [2] | BAYOU [3] |
| Genomic test components | *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*  And/or ≥ 10% genome-wide loss of heterozygosity  Or prior confirmation of a germline alteration in *BRCA1* or *BRCA2* | *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A, RAD51B*, *RAD51C*, *RAD51D*, *RAD54L* | *ATM*,  *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L* |
| Assay | FoundationOne  (Foundation Medicine, Cambridge, MA) | FoundationOne  (Foundation Medicine, Cambridge, MA) | FoundationOne  (Foundation Medicine, Cambridge, MA) |
| Tissue | Archival formalin-fixed, paraffin-embedded tumour sample | Archival formalin-fixed, paraffin-embedded tumour sample | Archival formalin-fixed, paraffin-embedded tumour sample |
| Biomarker positive rate | 29.8%  (74 of 248 patients screened within a multi-arm platform study, from which 40 were randomised) | 13% with ‘known’ pathogenic alterations  45% including variants of unknown significance  (from 47 (81%) patients from the trial ITT population with tissue available for analysis) | 20.1%  (31 of the 154 patient ITT population) |

ITT, intention to treat

Supplementary Table 2

Protocol defined secondary endpoints

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ATLANTIS [1] | Meet-URO12 [2] | BAYOU [3] | BAYOU biomarker positive subset [3] |
| Overall Survival | X | X\* | X |  |
| Patients alive at 18 months |  |  | X |  |
| Objective response rate | X | X\* | X | X |
| Maximum percentage decrease in measurable disease | X |  |  |  |
| Duration of response |  | X\* | X | X |
| Progression free survival |  |  |  | X |
| Progression-free survival at 6 months |  | X | X | X |
| Pharmacokinetics and immunogenicity |  |  | X |  |
| Health-related quality of life |  | X\* | X |  |
| Safety and tolerability | X | X | X |  |

\* Protocol defined secondary endpoint for which data are not yet reported

Supplementary Table 3.

Secondary endpoint efficacy outcomes

|  |  |  |  |
| --- | --- | --- | --- |
|  | ATLANTIS [1] | Meet-URO12 [2] | BAYOU [3] |
| Overall Survival | Median, rucaparib: not reached  Median, placebo: 72.3 weeks  (80% CI 51.7 to 85.4)  HR 1.22  (80% CI, 0.62 to 2.38; P = 0.35) | NR | Median, durvalumab + olaparib: 10.2 months  (95% CI, 7.0 to 13.9)  Median, durvalumab + placebo: 10.7 months  (95% CI, 7.2 to 17.3)  HR 1.07 (95% CI, 0.72 to 1.61; p = 0.728) |
| Response rate | 5% rucaparib  Zero placebo | NR | 28.2% durvalumab + olaparib  18.4% durvalumab + placebo  Odds ratio: 1.76  (95% CI, 0.82 to 3.78) |
| Duration of response | NE | NR | Durvalumab + olaparib: 32% at 12 months  Durvalumab + placebo: 64% at 12 months |

CI, confidence interval; NR, planned secondary endpoint that is not yet reported; NE, not evaluated as an endpoint in this study

Supplementary Table 4

Adverse events according to treatment arm allocation as per Common Terminology Criteria for Adverse Events

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ATLANTIS [1] |  | Meet-URO12 [2] |  | BAYOU [3] |  |
|  |  | Rucaparib  (N=19) | Placebo  (N=20) | Niraparib  (N=38) | BSC  (N=19) | Durvalumab + Olaparib  (N=76) | Durvalumab + Placebo  (N=76) |
| Lymphopenia | All grade | 15 (78.9) | 17 (85) | NR | NR | NR | NR |
|  | ≥ grade 3 | 0 | 0 | NR | NR | NR | NR |
| Anaemia | All grade | 15 (78.9) | 15 (75) | 19 (50) | 4 (21) | 18 (23.7) | 10 (13.2) |
|  | ≥ grade 3 | 1 (5.3%) | 0 | 4 (11%) | 0 | 5 (6.6%) | 1 (1.3%) |
| Fatigue | All grade | 12 (63.2) | 6 (30) | 12 (32) | 2 (11) | 12 (15.8) | 5 (6.6) |
|  | ≥ grade 3 | 1 (5.3) | 0 | 6 (16) | 1 (5) | 1 (1.3) | 0 |
| Low Phosphate | All grade | 11 (57.9) | 9 (45) | NR | NR | NR | NR |
|  | ≥ grade 3 | 0 | 0 | NR | NR | NR | NR |
| Nausea | All grade | 7 (36.8) | 1 (5) | 5 (13) | 0 | 15 (19.7) | 3 (3.9) |
|  | ≥ grade 3 | 0 | 0 | 1 (3) | 0 | 1 (1.3) | 0 |
| Rash | All grade | 4 (21.1) | 0 | 2 (5) | 0 | 7 (9.2) | 6 (7.9) |
|  | ≥ grade 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diarrhoea | All grade | 1 (5.3) | 2 (10) | 1 (3) | 0 | 8 (10.5) | 2 (2.6) |
|  | ≥ grade 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain | All grade | 1 (5.3) | 2 (10) | 3 (8) | 2 (11) | 2 (2.6) | 1 (1.3) |
|  | ≥ grade 3 | 0 | 0 | 0 | 0 | 1 (1.3) | 0 |
| Pruritus | All grade | 2 (10.5) | 0 | 1 (3) | 0 | 6 (7.9) | 8 (10.5) |
|  | ≥ grade 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Raised ALT | All grade | 11 (57.9) | 2 (10) | 3 (8) | 2 (11) | NR | NR |
|  | ≥ grade 3 | 0 | 0 | 0 | 0 | NR | NR |
| Raised ALP | All grade | 6 (31.6) | 3 (15) | NR | NR | NR | NR |
|  | ≥ grade 3 | 0 | 1 (5) | NR | NR | NR | NR |
| Hypertension | All grade | 2 (10.5%) | 3 (15%) | 2 (5) | 0 | NR | NR |
|  | ≥ grade 3 | 1 (5.3%) | 0 | 1 (3) | 0 | NR | NR |
| Anorexia | All grade | 3 (15.8) | 0 | 5 (13.2) | 0 | 8 (10.5) | 2 (2.6) |
|  | ≥ grade 3 | 0 | 0 | 1 (3) | 0 | 0 | 0 |
| Hyperkalaemia | All grade | 1 (5.3) | 2 (10) | 1(3) | 0 | NR | NR |
|  | ≥ grade 3 | 0 | 0 | 0 | 0 | NR | NR |
| Thrombocytopenia | All grade | NR | NR | 14 (36.8) | 1(5) | NR | NR |
|  | ≥ grade 3 | NR | NR | 6 (15.8) | 0 | NR | NR |
| Neutropenia | All grade | NR | NR | 8 (21.1) | 3(15.8) | 2 (2.6) | 0 |
|  | ≥ grade 3 | NR | NR | 2(5) | 1(5) | 2 (2.6) | 0 |
| Constipation | All grade | NR | NR | 12 (31.6) | 0 | 3 (3.9) | 2 (2.6) |
|  | ≥ grade 3 | NR | NR | 1 (3) |  | 0 | 0 |
| Mucositis | All grade | NR | NR | 5 (13.2) | 0 | 2 (2.6) | 0 |
|  | ≥ grade 3 | NR | NR | 1 (3) | 0 | 0 | 0 |
| Raised creatinine | All grade | NR | NR | 5 (13.2) | 1 (5) | 2 (2.6) | 2 (2.6) |
|  | ≥ grade 3 | NR | NR | 0 | 0 | 1 (1.3) | 0 |
| Increased AST | All grade | NR | NR | 2 (5) | 2 (11) | NR | NR |
|  | ≥ grade 3 | NR | NR | 0 | 0 | NR | NR |
| Haematuria | All grade | NR | NR | 6 (15.8) | 1 (5) | NR | NR |
|  | ≥ grade 3 | NR | NR | 2 (5) | 0 | NR | NR |
| Pain | All grade | NR | NR | 8 (21.1) | 6 (31.6) | NR | NR |
|  | ≥ grade 3 | NR | NR | 0 | 0 | NR | NR |
| Oedema | All grade | NR | NR | 1 (3) | 2 (10.5) | NR | NR |
|  | ≥ grade 3 | NR | NR | 0 | 0 | NR | NR |

All events reported in ≥ 10% of patients in one or more treatment arms in any trial are included. NR, not reported as an adverse event experienced by participants in this study; ALT, alanine aminotransaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase

References

[1] Crabb SJ, Hussain S, Soulis E, Hinsley S, Dempsey L, Trevethan A, et al. 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;41:54-64.

[2] Vignani F, Tambaro R, De Giorgi U, Giannatempo P, Bimbatti D, Carella C, et al. 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;83:82-9.

[3] Rosenberg JE, Park SH, Kozlov V, Dao TV, Castellano D, Li JR, et al. Durvalumab Plus Olaparib in Previously Untreated, Platinum-Ineligible Patients With Metastatic Urothelial Carcinoma: A Multicenter, Randomized, Phase II Trial (BAYOU). J Clin Oncol. 2023;41:43-53.