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Title: TOPARP-B: A Randomised Phase 2 Trial Evaluating Two Doses of Olaparib Against Metastatic Castration-Resistant Prostate Cancer With DNA Repair Gene Aberrations

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Abstract: Background
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Methods
In this randomised "pick-the-winner" phase 2 study we recruited participants from 17 UK hospitals. Men with progressing mCRPC following ≥1 taxane chemotherapy regimens and ECOG performance status ≤2 had tumour biopsy targeted sequencing. Patients with DDRga were randomised 1:1, by computer-generated minimisation method balancing for screening circulating tumour cell (CTC) count, to 400mg or 300mg olaparib twice daily, given continuously in 4-week cycles until disease progression or unacceptable toxicity. Neither participants nor investigators were blinded to dose allocation. The primary endpoint response rate (RR) was defined as a composite of radiological objective response (as assessed by Response Evaluation Criteria in Solid Tumors 1.1), prostate specific antigen decline of ≥50% (PSA50) from baseline and/or CTC count conversion (≥5 at baseline to <5/7.5ml blood). Confirmed response in consecutive assessment after >4 weeks was required for each component. Primary analysis was performed in the evaluable population. The trial aimed to exclude ≤30% confirmed RR in either arm. ClinicalTrials.gov, NCT01682772; recruitment completed and follow-up ongoing.

Findings
Overall, 711 patients consented for targeted screening between April 1 2015 and August 30 2018; 161 had DDRga; 98 were randomised and treated (49:49), with 92 evaluable for the primary endpoint (46:46). Median follow-up time was 24.8 months (Q1-Q3 16.7 to 35.9 months). Confirmed composite RRs were 54% (25/46, 95%CI 39-69%, meeting the threshold for primary endpoint) in the 400mg cohort, and 39% (18/46, 95%CI 25-55%) in the 300mg cohort. For each component, response rates were: radiological 400mg 8/33 (24%) vs 300mg 6/37 (16%); PSA50 400mg 17/46 (37%) vs 300mg 13/43 (30%); CTC count conversion 400mg 15/28 (54%), 300mg 13/27 (48%). The most common grade 3-4 adverse event in both cohorts was anaemia (300mg 15/46 [30.6%]; 400mg 18/46 [36.7%]). 19 serious adverse reactions in 10 patients were reported. One possibly treatment-related death (myocardial infarction) occurred after 11 days of treatment (300mg cohort).

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Olaparib has antitumour activity against mCRPC with DDRga, especially tumours with BRCA1/2 and PALB2 alterations, supporting implementation of mCRPC genomic stratification in clinical practice.

Funding
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***Reply to Reviewers Comments**

TOPARP-B MANUSCRIPT – RESPONSE TO EDITORIAL COMMENTS

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Comment #	**Comment**	**Author response and changes made**	**Page # in revised paper (clean version)**
1	Please provide the numbers at risk (numbers censored) for the ITT population in figure 3C.	The numbers at risk (numbers censored) for the ITT population have been added to figure 3C. A new figure 3C file has been uploaded.	N/A
2	Please upload a signed author contribution form for Dr Jain.	This has now been uploaded.	NA
3	Dr Chatfield's declaration in the text (no competing interests) does not match his ICMJE form (which has potential COIs). Please update this section of the manuscript or supply a new ICMJE form.	We have reviewed the declaration wording in the manuscript and it now matches with Mr Chatfield's COIs form.	38

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Joaquin Mateo[*], Nuria Porta[*], Diletta Bianchini, Ursula McGovern, Tony Elliott, Prof Robert Jones, Isabel Syndikus, Christy Ralph, Suneil Jain, Mohini Varughese, Omi Parikh, Simon Crabb, Angus Robinson, Duncan McLaren, Alison Birtle, Jacob Tanguay, Susana Miranda, Ines Figueiredo, George Seed, Claudia Bertan, Penny Flohr, Berni Ebbs, Pasquale Rescigno, Gemma Fowler, Ana Ferreira, Ruth Riisnaes, Rita Pereira, Andra Curcean, Robert Chandler, Matthew Clarke, Bora Gurel, Mateus Crespo, Daniel Nava Rodrigues, Shahneen Sandhu, Aude Espinasse, Peter Chatfield, Nina Tunariu, Wei Yuan, Prof Emma Hall[#], Suzanne Carreira[#] and **Prof Johann S. de Bono[#]**

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ABSTRACT

Background

Metastatic castration-resistant prostate cancer (mCRPC) is enriched in DNA damage repair (DDR) gene aberrations (DDRga). The TOPARP-B trial aims to prospectively validate the association between DDRga and response to olaparib in mCRPC.

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In this randomised "pick-the-winner" phase 2 study we recruited participants from 17 UK hospitals. Men with progressing mCRPC following ≥1 taxane chemotherapy regimens and ECOG performance status ≤2 had tumour biopsy targeted sequencing. Patients with DDRga were randomised 1:1, by computer-generated minimisation method balancing for screening circulating tumour cell (CTC) count, to 400mg or 300mg olaparib twice daily, given continuously in 4-week cycles until disease progression or unacceptable toxicity. Neither participants nor investigators were blinded to dose allocation. The primary endpoint response rate (RR) was defined as a composite of radiological objective response (as assessed by Response Evaluation Criteria in Solid Tumors 1.1), prostate specific antigen decline of ≥50% (PSA50) from baseline and/or CTC count conversion (≥5 at baseline to <5/7.5ml blood). Confirmed response in consecutive assessment after ≥4 weeks was required for each component. Primary analysis was performed in the evaluable population. The trial aimed to exclude ≤30% confirmed RR in either arm. ClinicalTrials.gov, NCT01682772; recruitment completed and follow-up ongoing.

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Olaparib has antitumour activity against mCRPC with DDRga, especially tumours with *BRCA1/2* and *PALB2* alterations, supporting implementation of mCRPC genomic stratification in clinical practice.

Funding

Cancer Research UK, AstraZeneca, Prostate Cancer UK, Prostate Cancer Foundation, Experimental Cancer Medicine Centres Network, and National Institute for Health Research Biomedical Research Centres.

INTRODUCTION

Molecular stratification for treatment is not currently standard-of-care for metastatic prostate cancers despite the elucidation of marked inter-patient genomic heterogeneity. Most therapeutic strategies for advanced prostate cancers target androgen receptor signalling; taxane-based chemotherapies and radiopharmaceuticals are also approved[1]. While these agents have improved outcomes in the last decade, metastatic prostate cancer remains invariably fatal and new therapeutic molecularly-stratified strategies are urgently needed. Genomic studies of metastatic prostate cancer have identified multiple potentially actionable recurrent genomic aberrations[2-4], including loss-of-function alterations in DNA repair genes in 20-25% of cases, including defects in homologous recombination mediated repair genes [3]. Among these, germline or somatic alterations in *BRCA2* are the commonest, accounting for 6-12% of cases across studies. These data underpin the evaluation of poly-(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors in this disease[5,6].

Olaparib is an orally-bioavailable inhibitor of the catalytic activity of PARP1 and PARP2, which have key roles in DNA defect repair (DDR). Olaparib is approved for the treatment of advanced ovarian and breast cancers associated with germline *BRCA1* or *BRCA2* mutations[7]. It is also approved as maintenance therapy after response to platinum-based chemotherapy for ovarian cancer, indicating benefit from PARP inhibition beyond tumours with *BRCA1/2* mutations [8,9]. Further, olaparib has antitumour activity in *in-vitro* and *in-vivo* models defective in other DDR proteins including *PALB2*, *ATM*, *FANCD2*, *RAD51*, *RAD54* and others, although the magnitude of preclinical sensitization varies between proteins, with *BRCA2* loss being arguably the most potent sensitizing event[10,11].

To evaluate the antitumour activity of olaparib against metastatic castration resistant prostate cancer (mCRPC), we designed TOPARP, an adaptive program of serial phase 2 clinical trials aimed at identifying predictive biomarkers for response to PARP inhibition in mCRPC. In the first trial, TOPARP-A, we identified an association between putatively deleterious DDRga and response to olaparib in 49 molecularly unselected patients[12]. We present here the results of TOPARP-B, designed to validate the observed antitumour activity in mCRPC patients with DDRga. Two different dose levels of olaparib were explored: 400mgs twice daily (BID) as used in TOPARP-A, and 300mg BID, the approved dose for ovarian and breast cancers[13].

METHODS

Study design and participants

TOPARP-B is a multi-centre, open-label, investigator-initiated randomised phase 2 trial where patients with tumours known to have deleterious DDRga that may sensitize to PARP inhibition were randomised to receive olaparib at either 300 mg BID or 400 mg BID tablets. Patients were recruited from 17 UK hospitals (appendix p 2) and molecularly pre-selected based on targeted next-generation sequencing (NGS) of primary or metastatic prostate cancer biopsies. Eligible patients were men aged 18 years or older, with histologically confirmed prostate adenocarcinoma that had developed metastasis and castration-resistance, whose tumours had a putatively pathogenic mutation or homozygous deletion in a DDR gene that could be associated with sensitivity to PARP inhibition. Patients were required to have previously received at least one but no more than two taxane-based chemotherapy regimens, regardless of prior exposure to novel hormonal agents. Other inclusion criteria included: documented prostate cancer progression at trial entry either by prostate-specific antigen (PSA, according to the PCWG2 criteria[14]), and/or radiologically (according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[15] or by bone scan as per PCWG2 criteria); castrate testosterone levels of <50 ng/dL; Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2; adequate organ function (including haemoglobin ≥9g/dL after protocol amendment in March 15, 2018 (previously ≥10g/dL), platelets ≥100x109/L, serum creatinine ≤1.5 x times above institutional range of normal values and albumin >25 g/dl). Patients previously treated with PARP inhibitors, platinum, cyclophosphamide or mitoxantrone were not eligible, as well as patients with known symptomatic brain metastasis or untreated cord compressions. Baseline count for circulating tumour cells (CTC) (CellSearch® system [Menarini

Silicon Biosystems, Inc, Bryn Athin, USA]) had to be ≥5 cells/7.5 ml blood except for patients with radiologically measurable target lesions ≥2cm in diameter on the baseline CT scan. A full list of inclusion/exclusion criteria, as well as the complete study protocol, is available in the appendix (pp 3-4, 20-148).

Patients provided written informed consent before enrolment, both for the NGS pre-screening and treatment stages. The study was approved by the London, Surrey Borders, Research Ethics Committee (REC reference 11/LO/2019), and co-sponsored by The Royal Marsden Hospital and The Institute of Cancer Research (ICR), London, UK. The trial was conducted in accordance with the principles of good clinical practice and overseen by Independent Data Monitoring (IDMC) and Trial Steering (TSC) committees. A Trial Management Group was responsible for the day-to-day running of the trial. The Clinical Trials and Statistics Unit at the ICR (ICR-CTSU) had overall responsibility for trial coordination, monitoring and analysis.

Randomisation and masking

Patients were registered into the trial for NGS pre-screening, and subsequently, eligible patients were randomly allocated (1:1) to olaparib 300mg BID or olaparib 400mg BID. Randomisation was done centrally by the ICR-CTSU via telephone. The allocation sequence was generated centrally by computer-generated minimisation algorithm derived by ICR-CTSU, with CTC count at screening (≥5 or < 5 cells/7.5 ml blood) as a balancing factor. ICR-CTSU staff involved in the randomisation service were not involved in the clinical running of the trial or data collection. Neither participants nor clinicians were blinded to dose allocation.

Procedures

In the pre-screening part of the study, primary and/or metastatic prostate cancer samples were acquired to identify tumours with putatively deleterious DDRga by targeted NGS at the Cancer Biomarkers Laboratory at The ICR. DNA was extracted from formalin-fixed and paraffin embedded (FFPE) tumour blocks using the FFPE Tissue DNA kit (Qiagen). Samples that passed quality control criteria were used for library preparation using a customized panel (Generead DNAseq Mix-n-Match Panel v2; Qiagen) covering 113 genes; libraries were read using a MiSeq Sequencer (Illumina). Expanded details on sample processing, quality check, and bioinformatics pipelines, as well as the panel design, are available in the appendix (pp 5-7).[16] Patients previously known to have germline aberrations were eligible only upon confirmatory tumour NGS testing.

All patients received olaparib at either of the allocated dose levels (300 and 400mgs BID) continuously in 4-week cycles until evidence of radiographic progression, unacceptable toxicity or patient decision to discontinue. Discontinuation due to clinical progression was based on treating clinician decision; discontinuation based solely on a rising PSA in the absence of radiographic or clinical progression was discouraged. Patients treated with 300mg BID were allowed to increase the olaparib dose to 400mg BID at confirmation of disease progression, providing this was considered clinically indicated by the treating physician and the patient had not previously required a dose reduction for management of toxicity.

Clinical assessments, including review of adverse events, performance status, physical examination and routine blood tests (haematology and biochemistry) took place after 2-weeks of starting treatment, and then at the start of every new 4-weekly cycle.

Radiological assessments (CT scan, bone scan) were performed every 12-weeks. CTC counts were measured every cycle for the first 12-weeks, and thereafter every 12-weeks. CTC counts were centrally analysed, and were not made available to the treating physician. PSA assessment was collected every cycle if available, and every 12-weeks as a minimum. Blood samples for correlative biomarker studies were taken on a 4-weekly basis. Repeated tumour biopsies were optional, and pursued when feasible at baseline, after 1-4 weeks on therapy and at the time of progression. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4. Guidelines on drug interruptions or dose reductions for haematological and non-haematological toxicities were implemented as outlined in the protocol (appendix pp 20-148). Up to 42-days of temporary interruption of treatment was allowed prior to mandating permanent discontinuation.

Outcomes

The primary endpoint was confirmed tumour response, defined as a composite of: objective response by RECIST 1.1 (with PCWG2 caveats) and/or PSA decline of ≥50% from baseline and/or conversion of CTC count from ≥5 cells/7.5 ml blood at baseline to <5 cells/7.5 ml[17]. To be considered a response for the primary analysis, at least one of these three tumour response components, confirmed in a second consecutive assessment obtained four or more weeks later, was required.

Protocol-defined secondary endpoints were: radiographic progression-free survival (rPFS), defined as time from randomisation to first evidence of radiographic progression (by RECIST 1.1 or bone scan as per PCWG2 criteria) or death; time to radiographic progression, defined as time from randomisation to first evidence of

radiographic progression; progression-free survival, defined as time from randomisation until radiographic progression, unequivocal clinical progression or death; overall survival (OS), defined as time from randomisation to death by any cause; time to PSA progression, defined as a confirmed ≥25% increase and absolute increase of ≥ 2 ng/mL in PSA above the nadir (PCWG2); duration of PSA response, defined as the time from the first documented ≥50% decline to PSA progression; best percentage change in PSA from baseline whilst on treatment, percentage change in PSA from baseline at 12 weeks (or earlier if discontinued therapy); proportion of patients with CTC conversion; and the safety and tolerability profile of olaparib in men with mCRPC. Pre-specified exploratory endpoints included the evaluation of response in patients who escalated dose to 400mg BID after progression on 300mg BID. A pharmacokinetics sub-study was planned but due to challenges in recruitment it was closed prematurely with no analyses pursued.

Statistical Analysis

Patients were randomised to either 400mg or 300mg BID of olaparib, under a "pick-the-winner" design[18]. Each dose cohort was assessed independently for the primary endpoint. The sample size to demonstrate the minimum desired antitumour activity was based on a one-stage A'Hern design, with RR≤30% for the null hypothesis, and RR>50% for the alternative hypothesis (one-sided alpha level 0.05; beta level 0.15). If at least 19/44 evaluable patients in a dose cohort responded (43%), then the dose cohort would be considered successful. If the 400 mg BID dose cohort was deemed successful, the biomarker identified in TOPARP-A, where all patients received 400mg BID, would be considered validated. In the event of both dose cohorts being successful, the pick-

the-winner selection strategy would include consideration of secondary endpoints. No formal interim analyses were planned.

For the primary endpoint, the evaluable population was defined as all randomised patients who met all of the inclusion and exclusion criteria, and commenced trial treatment, unless they discontinued treatment prior to 12-weeks for reasons that were not drug or disease related. Sensitivity analyses of the primary endpoint on the ITT (all randomised patients) and per protocol (all evaluable patients who received at least one cycle of olaparib, and had no major protocol violations) populations were conducted. A post-hoc sensitivity analysis on patients with CTC count $\geqq$5 cells/7.5ml blood at baseline was performed for comparison with TOPARP-A results. All other efficacy analyses were performed on the ITT population.

Analysis of the primary endpoint was triggered when all patients had completed at least 6-months of treatment (in the absence of prior discontinuation). Evaluable patients who discontinued prior to 12-weeks due to progression or toxicity and had no follow-up assessments for the primary endpoint were considered non-responders. Response rates are presented along with exact two-sided 95% confidence intervals. Local radiological response assessment was used for the primary endpoint definition; all RECIST 1.1 responses were confirmed by central review. Percentage changes from baseline in PSA levels and sum of target lesions, are represented in waterfall plots. Time-to-event endpoints are summarised by Kaplan-Meier curves, and median times estimated with 95% confidence intervals. For rPFS and PFS, patients alive and without progression were censored at the last scheduled disease assessment on study. For time to radiographic progression, patients who did not progress radiologically were censored at

the last scheduled disease assessment on study or date of death, whichever occurred earlier. Patients alive at the end of follow-up were censored for the analysis of OS. Landmark analyses were used to explore the association between CTC conversion at 8- and 12-weeks and rPFS and OS.

Subgroup analysis based on different genes of interest were pre-planned for efficacy endpoints. Five non-mutually exclusive subgroups were predefined: patients with alterations in *BRCA1*/*BRCA2*; *ATM*, *CDK12*, *PALB2*, and, lastly, patients with alterations in any other gene related to DDR or associated to PARPi sensitivity. Patients that had more than one DDRga were included in the analysis of all relevant subgroups.

Toxicity was analysed on all patients who received at least one dose of olaparib, and worst grades of adverse events (AEs) during treatment for each dose cohort are reported. Serious AEs and deaths observed within 30-days of the last dose of study treatment were summarised by dose cohort, as well as the exposure to study drug and reasons for discontinuation, dose modification or interruption and /or treatment delay.

The trial was not powered for head-to-head direct comparisons of the two dose-cohorts, so tests to compare them are considered hypothesis-generating (e.g. Chi-square test to compare response rates, and log-rank test to compare Kaplan-Meier curves). Further exploratory analyses are planned in the protocol and will be reported elsewhere. Statistical analyses were conducted with the use of Stata software (version 15), on a snapshot of the data taken on July 5, 2019. The Statistical Analysis Plan is available in the appendix (pp 149-177)**.**

This study was registered with ClinicalTrials.gov (NCT01682772) and on the European Clinical Trials database (EudraCT 2011-000601-49).

Role of the funding sources

The funders had no role in the study design, data collection, analysis and interpretation, or in the preparation of the report. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

RESULTS

Between April 1 2015 and August 30 2018, 711 patients consented for NGS pre-screening (Figure 1A). For 30 (4.2%) patients, no samples were made available for testing. From 681 patients with at least one sample available, 779 tumour samples were analysed (637 [82%] primary tumour samples, 142 [18%] post-castration resistance metastatic biopsies). For 89 (13%) patients, biomarker determination was not possible due to the sample, or the sequencing data, not fulfilling quality control parameters.

Of the 592 patients with evaluable tissue samples, 161 (27%) had DDRga based on NGS, while 431 (73%) did not. An oncoprint summarizing all alterations detected in the pre-screening phase of the study is presented in the appendix (p 14)**.** The commonest detected DDRga were mutations or homozygous deletions in *BRCA2* (44/592, 7.4%), *ATM* (40/592, 6.8%) and *CDK12* (33/592, 5.6%).

Ninety-eight DDRga patients were randomised and treated in the two dose-level cohorts (49 patients in each cohort). At the time of data snapshot, two patients remained on olaparib treatment. More participants were recruited than originally planned, at the recommendation of the IDMC, to account for six participants (three in each cohort) who were deemed not evaluable (determined ineligible post-randomisation) for the primary endpoint analyses. Median follow-up was 24.8 months (Q1-Q3 16.7 to 35.9 months).

Patients baseline characteristics are shown in Table 1; all had previously received docetaxel, and 88 (90%) had also been treated with abiraterone acetate (46) and/or enzalutamide (56) prior to study entry. The commonest sites for metastases at trial entry were bone (82; 84%) and lymph nodes (66; 67%), with measurable soft-tissue disease

being present in 75 (77%) patients. The distribution of gene subgroups was largely similar between the two dose cohorts, except for *CDK12* alterations which was imbalanced (31% 300mg vs 12% 400mg). The composition of pre-specified gene subgroups per cohort is shown in Figure 1B. Baseline features for each gene subgroup are summarised in the appendix (p 8).

For the 92 patients in the evaluable population for the primary endpoint, 70 (76%), 89 (97%) and 55 (60%) were evaluable for the RECIST 1.1, PSA, and CTC conversion components of the response definition respectively. The confirmed composite response rates were 25/46 (54%; 95%CI 39-69%) in the 400mg cohort, and 18/46 (39%; 95%CI 25-55%) in the 300mg cohort (p-value p=0.14) (Table 2***).*** For each component of the primary endpoint, response rates were: radiological response 400mg 8/33 (24%) vs 300mg 6/37 (16%); PSA response 400mg 17/46 (37%) vs 300mg 13/43 (30%).; CTC count conversion 400mg 15/28 (54%), 300mg 13/27 (48%). Based on the first 44 evaluable patients included in each cohort (as planned initially), there were 25/44 confirmed responses in the 400mg BID cohort, and 18/44 confirmed responses in the 300mg BID cohort; hence, the predefined criteria for success was met for 400mg BID but not for 300mg BID.

When considering only the 55 evaluable patients with $\geq$5 CTC/7.5ml blood at baseline, confirmed composite response rates were 61% (17/28, 95%CI 41-79%) in the 400mg cohort, and 48% (13/27, 95%CI 29-68%) in the 300mg cohort (see appendix p 9 for each individual component). In keeping with previous reports[17,19], CTC conversions post-treatment significantly associated with longer rPFS and OS in landmark analyses (appendix p 15).

Maximum change from baseline in PSA and sum of target lesions while on allocated treatment are presented in Figure 2A and 2B. Overall, 45 ITT patients at 400mg (92%) and 46 ITT patients at 300mg (94%) had radiographic progression or death; median rPFS was 5.5 months (95%CI 4.4-8.3) in the 400mg cohort, and 5.6 months (95%CI 3.7-7.7) in the cohort (Figure 2C). At the time of analyses, 39 400mg (80%) and 38 300mg (78%) patients were deceased, with a median overall survival of 14.3 months (95%CI 9.7-18.9) in the 400mg cohort and 10.1 months (95%CI 9-17.7) in the 300mg cohort. Further results on the secondary endpoints are summarised in the appendix (pp 16-18). Time on treatment for each patient is represented in Figure 2D**.** A summary of treatment dose reductions, interruptions and discontinuations by dose cohort is presented in the appendix (p 10).

Dose escalation from 300 mg to 400 mg was pursued in 11 patients; at the time of the data snapshot, 10 had discontinued treatment: two due to adverse events and eight for disease progression. These 11 patients were on treatment with 400mg for a median of 7.8 weeks (Q1-Q3: 3.7-10.4). None of these patients achieved a response after dose-escalation.

The confirmed composite response rates, and by individual components, for each of the predefined gene subgroups are shown in Table 2**.** Further analysis of secondary endpoints per gene subgroup can be found in Figure 3 and appendix (pp 11, 19).

The *BRCA1/BRCA2* subgroup had the highest response rate (25/30, 83%, 95%CI 65-94%), and the longest median rPFS of all DDRga subgroups (8.3 months, 95%CI 5.5-

13.0). The median OS for the *BRCA1/BRCA2* subgroup was 17.7 months (95%CI 9.9-22.2). Of the 32 patients included in this *BRCA1/BRCA2* subgroup, 13 had germline mutations in *BRCA2*, six somatic mutations in *BRCA2*, 11 homozygous deletions in *BRCA2*, and the remaining two cases had mutations in *BRCA1* (one germline, one somatic). Ten patients in the *BRCA1/BRCA2* subgroup (five allocated to 400mg BID, five allocated to 300mg BID) remained on treatment for over one year.

Twenty-one patients with suspected deleterious *ATM* aberrations were treated (one patient with homozygous deletion; the rest with germline or somatic mutations that are predicted to either result in truncation or missense mutations affecting the kinase domain). The composite response rate in patients with *ATM* aberrations was 37% (7/19; 95%CI 16-62%), with only 2 of those were RECIST/PSA responses (appendix p 12). Median rPFS and OS for the *ATM* altered subgroup were 5.8 months (95%CI 4.4-10.9) and 16.6 months (95%CI 8.9-24.2), respectively.

No confirmed PSA or RECIST responses were observed in the *CDK12* mutated subgroup, although 5/12 evaluable patients achieved a CTC conversion (including one with concomitant *BRCA1/2* alteration) (appendix pp 13). Median rPFS was 2.9 months (95% CI 2.6-7.5) and median OS was 9.5 months (95%CI 8.2-10.1).

Conversely, 4/7 (57%; 95%CI 18-90%) patients with *PALB2* mutations responded to treatment, all four had confirmed PSA responses, and two of them also had confirmed radiological responses. The median rPFS and OS in this subgroup were 5.3 months and 13.9 months respectively (95% CI could not be estimated due to small number of patients/events).

Lastly, 21 patients were evaluated as part of the subgroup with "other gene alterations". The composite response rate in this subgroup was 20% (4/20 patients, 95%CI 6-44), with median rPFS of 2.8 months (95%CI 2.6-4.3) and median OS of 7.7 months (95%CI 4.3-19.1). PSA responses were seen in one patient whose tumour had a somatic nonsense mutation in *FANCA* and one patient with a *CHEK2* mutation.

The safety population included all 98 patients treated. The tolerability profile was in line with what has been previously reported for olaparib and other PARP inhibitors[20-22] (Table 3). Anaemia was the most common treatment-emergent adverse event (69%), with 34% experiencing G3-4 anaemia. Fatigue was also common (54.1%; 7% grade 3-4). Grade 3-4 gastrointestinal toxicities were rare (1% nausea, 2% decreased appetite, 2% diarrhoea). Anaemia was the commonest AE leading to dose reductions; 18 (37%) patients in the 400mg cohort, and six (12%) in the 300mg cohort, required at least one dose reduction (appendix p 10). Eight patients achieving a response while on 400mg, continued to respond for more than 6-months after dose reduction to 300mg or lower. Overall, 18/98 (19%) patients were permanently discontinued from olaparib treatment due to AE.

A total of 107 serious adverse events were reported in 49 (50%) patients, with 19 serious adverse reactions (SAR, possibly related to study drug, 11 in 300mg, 8 in 400mg) in 13 patients. The commonest SAR was anaemia (6 in 300mg, 5 in 400mg). Four SAR were considered suspected unexpected (SUSAR, two in each dose cohort group), including a patient diagnosed with myelodysplasia after 6.5 months of 300mg olaparib. This patient developed acute myeloid leukaemia after olaparib discontinuation.

One 300mg patient (2%) died due to a myocardial infarction, assessed as possibly drug related, after 11-days of treatment. All other deaths were unrelated to treatment.

DISCUSSION

TOPARP-B has confirmed the antitumour activity of olaparib against metastatic prostate cancers (mPC) with specific DDRga. The number of composite responses observed in the 400mg BID cohort met the predefined criteria for success, validating the biomarker identified in TOPARP-A[12]. Overall, the data suggest that both drug dose and the specific DDR gene aberration type may matter to antitumour activity since the composite response rate at the 300mg BID was lower and did not reach predefined criteria for success. The antitumour activity observed varied considerably for different DDRga, with the most impressive antitumour activity seen in the *BRCA1/BRCA2*-altered subgroup.

Despite randomisation, there was an imbalance in *CDK12* aberrations between cohorts, with an enrichment for these in the 300mg cohort. This may explain, at least in part, the inferior composite response rate in the 300mg cohort[4,23]. The rationale to explore these two dose levels originated from prior clinical observations indicating a dose-response relationship for olaparib between 100mg BID and 400mg BID, although this dose increase is associated with increased toxicity [24,25]. In keeping with this, 37% patients at 400mg BID had to dose reduce to 300mg BID, most commonly due to anaemia; all these data would need to be considered when assessing the optimal dose of olaparib for prostate cancer care.

These results support the implementation of routine genomic testing of metastatic prostate cancer, to detect DNA repair defects for PARP inhibition. In previous studies, we reported an enrichment for germline inherited mutations in DDR genes in this mCRPC population[26], which has led to a recommendation of broad germline NGS

testing for all men suffering from mPC per NCCN guidelines. The antitumour activity demonstrated herein for olaparib in mCRPC patients with both germline and somatic aberrations of *BRCA2* now supports the implementation of NGS testing of tumour samples.

Antitumour activity was also observed in other DDRga subgroups. Responses in tumours with *PALB2* mutations were frequent (4/7 patients), although the low prevalence of these mutations means that further data are required to confirm these findings. Clinical qualification of low-prevalence biomarkers is challenging in the pursuit of precision medicine approaches; the validation of genomic signatures[23,27] or functional biomarkers[28] that identify tumours with defective homologous-recombination, regardless of the mutated gene of origin, could help move the field forward, but such assays have not been yet validated in prostate cancer.

Conversely, germline and somatic *ATM* aberrations are common in mPC; *ATM* functions as a cell cycle checkpoint, preventing cell cycle progression in the presence of DNA damage rather than directly mediating repair unlike *BRCA2* and *PALB2*. In the TOPARP-A trial, 5 patients had *ATM* aberrations in tumour biopsies: 2 of these had a PSA response, and a further 2 achieved a CTC conversion. Preliminary reports suggest that rucaparib, another PARP inhibitor, resulted in few PSA falls in patients with *ATM* aberrations[29]. In TOPARP-B, we treated 21 patients with suspected deleterious *ATM* aberrations; two of them achieved a RECIST/PSA response, and several others had CTC counts conversions following therapy. CTC count falls seen in this sub-group associated with longer duration on trial, tumour shrinkage by RECIST and PSA falls (appendix p 12), as was the case for the overall TOPARP-B population, with CTC

conversions robustly associating with longer rPFS and OS. Overall, these data indicate that the antitumour activity of olaparib in *ATM* loss mCRPC is less than that for *BRCA* altered tumours; nevertheless, a subset of these patients with *ATM* altered mCRPC appear to derive benefit. Detection of *ATM* alterations alone may, however, be insufficient to identify these sensitive tumours. Further studies, as well as the study of rational drug combinations, are now needed to elucidate how to best evaluate and treat mCRPC with *ATM* alterations. Ongoing exploratory analysis from this trial will look into further characterization of exceptional responses within each gene-defined subgroup to optimize patient stratification.

We do acknowledge limitations to this study. While the utilization of targeted NGS facilitates the clinical implementation of patient stratification, this may be insufficient to capture more complex aberrations resulting in PARPi sensitivity. Moreover, as all patients in this study had DDRga and received olaparib, we are not able to fully differentiate the predictive value versus the prognostic impact on of the survival data. Randomised trials including biomarker-positive and biomarker-negative patients are more able to clinically qualify a putative predictive biomarker.

Nonetheless, these TOPARP results have overall driven the design and conduct of multiple registration trials of PARP inhibitors in mCRPC that are likely to guide the clinical use of PARP inhibitors in mPC in the future. Most of these studies aim to validate PARP inhibition as a precision medicine strategy for prostate cancers with DDRga; other studies, in parallel, explore the addition of PARP inhibitors to standard-of-care AR targeting agents, based on results from a phase II clinical trial which has

been reported to indicate that a broader target population may benefit from these agents[30].

In conclusion, these TOPARP-B data have confirmed the antitumour activity of olaparib against mPC with certain DDRga. The high response rates observed in patients with mCRPC with germline or somatic *BRCA1/2* aberrations, and the durability of many of these responses, support the use of olaparib in this sub-population. The antitumour activity observed against tumours with *ATM, PALB2*, *FANCA* or *CHEK2* aberrations suggest that PARPi may have a role as a single agent or in rational combinations against these other mPC subtypes, although further data are needed to precisely assess the clinical relevance of each of these different DDRga in prostate cancer.

Figure legends

Figure 1. (A) CONSORT Flow diagram of patient disposition in the TOPARP-B trial (B) Oncoprint of mutations and homozygous deletions in DDR genes that led to trial inclusion for the IIT population (n=98)**.

DDRga= Defective DNA Repair Gene aberration

** Non-mutually exclusive subgroups: One patient treated at 300mgs BID had BRCA1/2, CDK12 & 'Other mutations' (300mg); two further 300 mg patients had both PALB2 & 'Other mutations'.*

*** The BRCA2 K3226* variant was not considered sufficient for patients to be considered eligible; however, one patient with a BRCA2 K3226* variant was included due to evidence of concomitant loss of the contralateral allele.*

Figure 2. Antitumour activity by allocated dose cohort (IIT population): (A) Best percentage change from baseline in PSA whilst on allocated treatment; (B) Best percentage change from baseline in sum of target lesions (RECIST 1.1) whilst on allocated treatment; (C) Radiographic Progression-Free Survival; (D) Swimmers plot of time on treatment for each patient, indicating periods of treatment interruptions, dose reductions or dose-escalations (in the 300mg dose cohort).

Figure 3. Antitumour activity by gene subgroup (IIT population, pooled 300mg and 400mg BID cohorts): (A) Best percentage change from baseline in PSA whilst on allocated treatment; (B) Best percentage change from baseline in sum of target lesions (RECIST 1.1) whilst on allocated treatment; (C) Radiographic Progression-Free Survival; (D) Swimmers plot of time on treatment for each patient.

(*) indicate patients with different mutations qualifying for more than one subgroup.

Table 1. Baseline characteristics of TOPARP-B patients in the ITT population, presented by dose cohort

	Total (N=98)		**Dose group**			
			300 mg (N=49)		**400 mg (N=49)**	
Age at trial entry, mean (SD)	67.6 (7.6)		67.7 (7.4)		67.4 (7.8)	
Years from initial diagnosis - median (Q1-Q3)	4.6 (2.8-7)		3.5 (2.4-6.4)		5.2 (3.6-7.3)	
Years from diagnosis of CRPC - median (Q1-Q3)	2.6 (1.6-4)		2.4 (1.2-3.7)		3.0 (1.8-4)	
Metastatic disease at diagnosis, n (%)						
Yes	49	(50%)	24	(49%)	25	(51%)
No	45	(45.9%)	24	(49%)	21	(42.9%)
Not available	4	(4.1%)	1	(2%)	3	(6.1%)
Gleason score at diagnosis, n (%)						
≤7	19	(19.4%)	4	(8.2%)	15	(30.6%)
≥8	71	(72.4%)	42	(85.7%)	29	(59.2%)
Not available	8	(8.2%)	3	(6.1%)	5	(10.2%)
Previous treatment for PC, n (%)						
Prostatectomy	13	(13.3%)	7	(14.3%)	6	(12.2%)
Radical radiotherapy	43	(43.9%)	22	(44.9%)	21	(42.9%)
Biphosphonates	4	(4.1%)	2	(4.1%)	2	(4.1%)
Radium 223	*14*	*(14.3%)*	*6*	*(12.2%)*	*8*	*(16.3%)*
Docetaxel	98	(100%)	49	(100%)	49	(100%)
Cabazitaxel	37	(37.8%)	15	(30.6%)	22	(44.9%)
Abiraterone	46	(46.9%)	24	(49%)	22	(44.9%)
Enzalutamide	56	(57.1%)	27	(55.1%)	29	(59.2%)
Abiraterone and/or Enzalutamide	88	(89.8%)	43	(87.8%)	45	(91.8%)
Evidence of progression at trial entry, n (%)						
PSA only	27	(27.6%)	15	(30.6%)	12	(24.5%)
Radiographic progression (+/- PSA progression)	71	(72.4%)	34	(69.4%)	37	(75.5%)
Site of metastatic disease at trial entry, n (%) [(1)]						
Lung	8	(8.2%)	4	(8.2%)	4	(8.2%)
Lymph nodes	66	(67.3%)	34	(69.4%)	32	(65.3%)
Liver	23	(23.5%)	11	(22.4%)	12	(24.5%)
Bone	82	(83.7%)	41	(83.7%)	41	(83.7%)
PSA at trial entry (ng/ml) – median (Q1-Q3)	154.8 (45.5-472.0)		151.5 (49.0-446.0)		158.0 (45.5-472.0)	
CTC count at trial entry, n (%)	**n**	**%**	**n**	**%**	**n**	**%**
CTC<5	34	(34.7%)	17	(34.7%)	17	(34.7%)

	Total (N=98)		Dose group			
			300 mg (N=49)		400 mg (N=49)	
CTC >= 5	63	(64.3%)	31	(63.3%)	32	(65.3%)
Not available [2]	1	(1%)	1	(2%)	0	(0%)
RECIST soft tissue disease, n (%)						
Bone lesions only	10	(10.2%)	5	(10.2%)	5	(10.2%)
Non-measurable disease only (+/- bone lesions)	13	(13.3%)	5	(10.2%)	8	(16.3%)
Measurable disease (+/- bone lesions)	75	(76.5%)	39	(79.6%)	36	(73.5%)
DDRga gene subgroup, n (%)[3]	**n**	**%**	**n**	**%**	**n**	**%**
BRCA1/2	32	(32.7%)	15	(30.6%)	17	(34.7%)
ATM	21	(21.4%)	10	(20.4%)	11	(22.5%)
CDK12	21	(21.4%)	15	(30.6%)	6	(12.4%)
PALB2	7	(7.1%)	3	(6.1%)	4	(8.2%)
Other	21	(21.4%)	10	(20.4%)	11	(22.5%)

Q1: 25% percentile, Q3: 75% percentile

(1) More than one site could be reported.

(2) Screening CTC assessment not possible due to CTC kit shortage. Patient allowed to be randomised as he had RECIST 1.1 measurable disease; for randomisation CTC assumed <5 but patient was unevaluable for CTC response.

(3) Non-mutually exclusive subgroups: one 300mg cohort patient had *BRCA1/2, CDK12* and 'Other mutations', and two 300 mg cohort patients with *PALB2* mutations also had other mutations (in *MSH2* and *NBN* respectively).

Table 2. Overall antitumour activity in patients with DDRga, by dose cohort and by gene subgroup (evaluable population; confirmed responses)

	Composite overall response			RECIST 1.1 Objective Response			PSA fall ≥50%			CTC conversion			RECIST 1.1 or PSA response		
	resp/n	**RR**	**95% CI**	**resp/n**	**%**	**95% CI**	**resp/n**	**%**	**95% CI**	**resp/n**	**%**	**95% CI**	**resp/n**	**%**	**95% CI**
Evaluable patients	**43/92**	**46.7**	**36.3-57.4**	**14/70**	**20.0%**	**11.4-31.3**	**30/89**	**33.7%**	**24.0-44.5**	**28/55**	**50.9%**	**37.1-64.6**	***32/92***	***34.8%***	***25.1-45.4***
By dose cohort:															
300 mg BID	18/46	39.1	25.1-54.6	6/37	16.2%	6.2-32.0	13/43	30.2%	17.2-46.1	13/27	48.1%	28.7-68.1	*13/46*	*28.3%*	*16.0-43.5*
400 mg BID	25/46	54.3	39.0-69.1	8/33	24.2%	11.1-42.3	17/46	37.0%	23.2-52.5	15/28	53.6%	33.9-72.5	*19/46*	*41.3%*	*27.0-56.8*
By gene subgroup[¥]															
BRCA 1/2	25/30	83.3	65.3-94.4	11/21	52.4%	29.8-74.3	23/30	76.7%	57.7-90.1	17/22	77.3%	54.6-92.2	24/30	80.0%	61.4-92.3
ATM	7/19	36.8	16.3-61.6	1/12	8.3%	0.2-38.5	1/19	5.3%	0.1-26.0	5/10	50.0%	18.7-81.3	2/19	10.5%	1.3-33.1
CDK12	5/20	25.0	8.7-49.1	0/18	0.0%	0-18.5*	0/20	0.0%	0-16.8*	5/12	41.7%	15.2-72.3	0/20	0.0%	0-16.8*
PALB2	4/7	57.1	18.4-90.1	2/6	33.3%	4.3-77.7	4/6	66.7%	22.3-95.7	0/2	0.0%	0-84.2*	4/7	57.1%	18.4-90.1
Other	4/20	20.0	5.7-43.7	0/17	0.0%	0-19.5*	2/17	11.8%	1.5-36.4	3/11	27.3%	6.0-61.0	2/20	10.0%	1.2-31.7

Resp/n: number of observed responses / number of evaluable patients; RR: response rate, 95% CI: 95% confidence interval. *One-sided exact binomial 95% confidence intervals

[¥]Non-mutually exclusive subgroups: One patient treated at 300mgs BID had *BRCA1/2*, *CDK12* & 'Other mutations' (300mg); two further 300 mg patients had both *PALB2* & 'Other mutations'. These patients have been included in analysis for each subgroup separately. For the gene subgroup analyses, dose cohorts have been pooled.

Table 3 – Treatment emergent adverse events, by dose cohort

Any grade 1-2 event occurring in ≥10% of patients is reported. All grade 3, 4, and 5 events are reported.

*Includes one G5 event (myocardial infarction), grouped with G4 for conciseness.

	300mg (N=49)			400mg (N=49)		
MedDRA preferred term	**G2**	**G3**	**G4***	**G2**	**G3**	**G4**
Anaemia	16 (32.7)	14 (28.6)	1 (2.0)	19 (38.8)	18 (36.7)	0
Fatigue	19 (38.8)	3 (6.1)	0	27 (55.1)	4 (8.2)	0
Back pain	13 (26.5)	4 (8.2)	0	11 (22.4)	3 (6.1)	0
Nausea	17 (34.7)	1 (2.0)	0	13 (26.5)	0	0
Platelet count decreased	9 (18.4)	2 (4.1)	1 (2.0)	12 (24.5)	3 (6.1)	0
Decreased appetite	13 (26.5)	2 (4.1)	0	10 (20.4)	0	0
Vomiting	10 (20.4)	0	0	15 (30.6)	0	0
Weight decreased	9 (18.4)	1 (2.0)	0	15 (30.6)	0	0
Diarrhoea	8 (16.3)	1 (2.0)	0	10 (20.4)	1 (2.0)	0
Arthralgia	8 (16.3)	1 (2.0)	0	5 (10.2)	4 (8.2)	0
Hypertension	9 (18.4)	1 (2.0)	0	4 (8.2)	4 (8.2)	0
Neutrophil count decreased	9 (18.4)	2 (4.1)	0	4 (8.2)	2 (4.1)	1 (2.0)
Dyspnoea	5 (10.2)	1 (2.0)	0	10 (20.4)	1 (2.0)	0
Abdominal pain	4 (8.2)	0	0	6 (12.2)	5 (10.2)	1 (2.0)
Blood creatinine increased	9 (18.4)	0	0	6 (12.2)	0	0
Oedema peripheral	6 (12.2)	0	0	8 (16.3)	1 (2.0)	0
Urinary tract infection	3 (6.1)	3 (6.1)	0	6 (12.2)	3 (6.1)	0
Constipation	7 (14.3)	0	0	7 (14.3)	0	0
Cough	3 (6.1)	0	0	9 (18.4)	0	0
Musculoskeletal chest pain	3 (6.1)	0	0	9 (18.4)	0	0
Musculoskeletal pain	5 (10.2)	1 (2.0)	0	5 (10.2)	1 (2.0)	0
Hypokalaemia	3 (6.1)	0	0	8 (16.3)	0	0
Muscular weakness	4 (8.2)	0	0	5 (10.2)	2 (4.1)	0
WBC count decreased	4 (8.2)	0	0	6 (12.2)	1 (2.0)	0
AST increased	3 (6.1)	0	1 (2.0)	4 (8.2)	1 (2.0)	0
ALP increased	3 (6.1)	0	0	5 (10.2)	1 (2.0)	0
Dysgeusia	6 (12.2)	0	0	3 (6.1)	0	0
Haematuria	5 (10.2)	0	0	2 (4.1)	2 (4.1)	0
Influenza like illness	3 (6.1)	0	0	6 (12.2)	0	0
Muscle spasms	3 (6.1)	0	0	6 (12.2)	0	0

	300mg (N=49)			400mg (N=49)		
MedDRA preferred term	**G2**	**G3**	**G4***	**G2**	**G3**	**G4**
GGT increased	3 (6.1)	0	0	2 (4.1)	2 (4.1)	1 (2.0)
Lower resp. tract infection	4 (8.2)	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Lymphocyte count decreased	2 (4.1)	1 (2.0)	0	3 (6.1)	2 (4.1)	0
Pyrexia	4 (8.2)	2 (4.1)	0	2 (4.1)	0	0
ALT increased	2 (4.1)	0	0	3 (6.1)	2 (4.1)	0
Groin pain	3 (6.1)	0	0	2 (4.1)	2 (4.1)	0
Dizziness	2 (4.1)	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Spinal cord compression	0	1 (2.0)	0	0	5 (10.2)	0
Blood bilirubin increased	1 (2.0)	0	0	3 (6.1)	0	1 (2.0)
Cellulitis	2 (4.1)	0	0	2 (4.1)	1 (2.0)	0
Pain	1 (2.0)	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Hydronephrosis	1 (2.0)	2 (4.1)	0	0	1 (2.0)	0
Hyponatraemia	0	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Myocardial infarction	0	1 (2.0)	**2 (4.1)***	0	1 (2.0)	0
Acute kidney injury	1 (2.0)	0	1 (2.0)	1 (2.0)	0	0
Hyperkalaemia	0	1 (2.0)	0	2 (4.1)	0	0
Rectal haemorrhage	0	1 (2.0)	0	1 (2.0)	1 (2.0)	0
Amylase increased	0	0	0	1 (2.0)	1 (2.0)	0
Atrial fibrillation	0	0	0	1 (2.0)	1 (2.0)	0
Circulatory collapse	0	2 (4.1)	0	0	0	0
Confusional state	1 (2.0)	1 (2.0)	0	0	0	0
Femoral neck fracture	0	1 (2.0)	0	1 (2.0)	0	0
Femur fracture	0	0	0	0	2 (4.1)	0
Mobility decreased	1 (2.0)	0	0	0	1 (2.0)	0
Pneumonia	0	0	0	0	2 (4.1)	0
Presyncope	1 (2.0)	0	0	0	1 (2.0)	0
Pulmonary embolism	0	1 (2.0)	0	0	1 (2.0)	0
Respiratory tract infection	1 (2.0)	1 (2.0)	0	0	0	0
Abdominal infection	0	1 (2.0)	0	0	0	0
Acute myeloid leukaemia	0	0	1 (2.0)	0	0	0
Arthritis bacterial	0	1 (2.0)	0	0	0	0
Bronchitis	0	1 (2.0)	0	0	0	0
Cauda equina syndrome	0	0	0	0	1 (2.0)	0
Embolism	0	0	0	0	1 (2.0)	0
Enterocolitis infectious	0	0	0	0	1 (2.0)	0
Febrile neutropenia	0	0	0	0	1 (2.0)	0
Hip fracture	0	1 (2.0)	0	0	0	0
Intestinal obstruction	0	0	0	0	1 (2.0)	0

	300mg (N=49)			400mg (N=49)		
MedDRA preferred term	**G2**	**G3**	**G4***	**G2**	**G3**	**G4**
Jaundice	0	0	0	0	1 (2.0)	0
Neutropenic sepsis	0	0	0	0	1 (2.0)	0
Pyelonephritis	0	0	0	0	1 (2.0)	0
Radiculopathy	0	0	0	0	1 (2.0)	0
Renal colic	0	1 (2.0)	0	0	0	0
Sepsis	0	0	0	0	0	1 (2.0)
Ureteric obstruction	0	1 (2.0)	0	0	0	0
Urosepsis	0	1 (2.0)	0	0	0	0
Vascular pseudoaneurysm	0	0	1 (2.0)	0	0	0
Vision blurred	0	1 (2.0)	0	0	0	0

RESEARCH IN CONTEXT

Evidence before this study

Trials for advanced prostate cancer have rarely pursued molecular stratification, and none of the drugs approved up to date for metastatic prostate cancer care have a validated companion biomarker. Before starting this study, several genomic landscape studies were published describing an enrichment for aberrations in DNA repair genes in metastatic prostate cancers (studies identified in Pubmed, searching for "prostate cancer", "genomics", "biopsy", between 2010 and 2015). Preclinical and clinical studies identified in Pubmed (search for "cancer", "PARP" and "BRCA" or "DNA repair" between 2005 and 2019) have established a correlation between different DNA repair defects and sensitivity to PARP inhibition in different tumour types, leading to drug approvals in ovarian and breast cancer. In the TOPARP-A trial, we identified an association between somatic alterations in DNA repair genes and antitumour activity of olaparib in 49 patients with metastatic prostate cancer. Other clinical trials of PARP inhibitors in prostate cancer were identified using ClinicalTrials.gov website, searching for "prostate cancer" and "PARP".

Added value of this study

To our knowledge, this is the first ever prospective clinical trial for a genomically-defined population of metastatic prostate cancers. TOPARP-B aims to clinically qualify, for the first time, a predictive biomarker for treating metastatic prostate cancers. TOPARP-B also assessed different doses of olaparib, and correlated different genomic aberrations and antitumour activity. This study has confirmed the antitumour activity of olaparib against metastatic prostate cancer with defective DNA repair, secondary to either germline or somatic gene inactivation.

Implications of all the available evidence

Randomised phase III trials for DNA repair defective prostate cancers are now ongoing based on these data. Our results, if confirmed in registration studies, would support implementing tumour genomic testing in clinical practice for treatment stratification in advanced prostate cancer.

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Data sharing statement

The ICR-CTSU supports the wider dissemination of information from the research it conducts, and increased cooperation between investigators. Trial data is collected, managed, stored, shared and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and Intellectual Property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee as required.

Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymizing identifiable patient data. Additionally all indirect identifiers that may lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines.

AUTHOR CONTRIBUTIONS

JM – trial design, protocol development, data collection, participant recruitment, translational experiments, data interpretation, writing, Trial Management Group member; NP – trial design, protocol development, statistical analysis, data interpretation, writing, Trial Management Group member. DB – participant recruitment, data collection. UMG - participant recruitment, data collection, Trial Management Group member. TE - participant recruitment, data collection, Trial Management Group member. RJ – protocol development, participant recruitment, data collection, Trial Management Group member .IS- participant recruitment, data collection, Trial Management Group member. CR - participant recruitment, data collection, Trial Management Group member. SJ - participant recruitment, data collection, Trial Management Group member. MV - participant recruitment, data collection, Trial Management Group member. OP - participant recruitment, data collection, Trial Management Group member. SCr- participant recruitment, data collection, Trial Management Group member. AR - participant recruitment, data collection, Trial Management Group member. DML - participant recruitment, data collection, Trial Management Group member. AB - participant recruitment, data collection, Trial Management Group member .JT - participant recruitment, data collection. SM –data collection, sample processing, translational experiments, data analyses, Trial Management Group member. IF – data collection, sample processing, translational experiments, data analyses. GS –translational experiments, data interpretation, data analyses. CB - data collection, sample processing, translational experiments. PF – protocol development, data collection, data interpretation, data analyses. BE – data collection, sample processing, translational experiments. PR – patient recruitment, data collection. GF – data collection, sample processing, translational experiments. AF –

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Declaration of Interests

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The authors affiliated to The Institute of Cancer Research disclose that the institution is joint applicant for the patent entitled 'DNA damage repair inhibitors for treatment of cancer' which includes the granted application US8143241.

All other authors do not declare any potentially relevant conflict of interest.

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TOPARP-B: A Randomised Phase 2 Trial Evaluating Two Doses of Olaparib Against Metastatic Castration-Resistant Prostate Cancer With DNA Repair Gene Aberrations

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ABSTRACT

Background

Metastatic castration-resistant prostate cancer (mCRPC) is enriched in DNA damage repair (DDR) gene aberrations (DDRga). The TOPARP-B trial aims to prospectively validate the association between DDRga and response to olaparib in mCRPC.

Methods

In this randomised "pick-the-winner" phase 2 study we recruited participants from 17 UK hospitals. Men with progressing mCRPC following ≥1 taxane chemotherapy regimens and ECOG performance status ≤2 had tumour biopsy targeted sequencing. Patients with DDRga were randomised 1:1, by computer-generated minimisation method balancing for screening circulating tumour cell (CTC) count, to 400mg or 300mg olaparib twice daily, given continuously in 4-week cycles until disease progression or unacceptable toxicity. Neither participants nor investigators were blinded to dose allocation. The primary endpoint response rate (RR) was defined as a composite of radiological objective response (as assessed by Response Evaluation Criteria in Solid Tumors 1.1), prostate specific antigen decline of ≥50% (PSA50) from baseline and/or CTC count conversion (≥5 at baseline to <5/7.5ml blood). Confirmed response in consecutive assessment after ≥4 weeks was required for each component. Primary analysis was performed in the evaluable population. The trial aimed to exclude ≤30% confirmed RR in either arm. ClinicalTrials.gov, NCT01682772; recruitment completed and follow-up ongoing.

Findings

Overall, 711 patients consented for targeted screening between April 1 2015 and August 30 2018; 161 had DDRga; 98 were randomised and treated (49:49), with 92 evaluable for the

primary endpoint (46:46). Median follow-up time was 24.8 months (Q1-Q3 16.7 to 35.9 months). Confirmed composite RRs were 54% (25/46, 95%CI 39-69%, meeting the threshold for primary endpoint) in the 400mg cohort, and 39% (18/46, 95%CI 25-55%) in the 300mg cohort. For each component, response rates were: radiological 400mg 8/33 (24%) vs 300mg 6/37 (16%); PSA50 400mg 17/46 (37%) vs 300mg 13/43 (30%); CTC count conversion 400mg 15/28 (54%), 300mg 13/27 (48%). The most common grade 3-4 adverse event in both cohorts was anaemia (300mg 15/46 [30.6%]; 400mg 18/46 [36.7%]). 19 serious adverse reactions in 10 patients were reported. One possibly treatment-related death (myocardial infarction) occurred after 11 days of treatment (300mg cohort).

Interpretation

Olaparib has antitumour activity against mCRPC with DDRga, especially tumours with *BRCA1/2* and *PALB2* alterations, supporting implementation of mCRPC genomic stratification in clinical practice.

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INTRODUCTION

Molecular stratification for treatment is not currently standard-of-care for metastatic prostate cancers despite the elucidation of marked inter-patient genomic heterogeneity. Most therapeutic strategies for advanced prostate cancers target androgen receptor signalling; taxane-based chemotherapies and radiopharmaceuticals are also approved[1]. While these agents have improved outcomes in the last decade, metastatic prostate cancer remains invariably fatal and new therapeutic molecularly-stratified strategies are urgently needed. Genomic studies of metastatic prostate cancer have identified multiple potentially actionable recurrent genomic aberrations[2-4], including loss-of-function alterations in DNA repair genes in 20-25% of cases, including defects in homologous recombination mediated repair genes [3]. Among these, germline or somatic alterations in *BRCA2* are the commonest, accounting for 6-12% of cases across studies. These data underpin the evaluation of poly-(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors in this disease[5,6].

Olaparib is an orally-bioavailable inhibitor of the catalytic activity of PARP1 and PARP2, which have key roles in DNA defect repair (DDR). Olaparib is approved for the treatment of advanced ovarian and breast cancers associated with germline *BRCA1* or *BRCA2* mutations[7]. It is also approved as maintenance therapy after response to platinum-based chemotherapy for ovarian cancer, indicating benefit from PARP inhibition beyond tumours with *BRCA1/2* mutations [8,9]. Further, olaparib has antitumour activity in *in-vitro* and *in-vivo* models defective in other DDR proteins including *PALB2*, *ATM*, *FANCD2*, *RAD51*, *RAD54* and others, although the magnitude of preclinical sensitization varies between proteins, with *BRCA2* loss being arguably the most potent sensitizing event[10,11].

To evaluate the antitumour activity of olaparib against metastatic castration resistant prostate cancer (mCRPC), we designed TOPARP, an adaptive program of serial phase 2 clinical trials aimed at identifying predictive biomarkers for response to PARP inhibition in mCRPC. In the first trial, TOPARP-A, we identified an association between putatively deleterious DDRga and response to olaparib in 49 molecularly unselected patients[12]. We present here the results of TOPARP-B, designed to validate the observed antitumour activity in mCRPC patients with DDRga. Two different dose levels of olaparib were explored: 400mgs twice daily (BID) as used in TOPARP-A, and 300mg BID, the approved dose for ovarian and breast cancers[13].

METHODS

Study design and participants

TOPARP-B is a multi-centre, open-label, investigator-initiated randomised phase 2 trial where patients with tumours known to have deleterious DDRga that may sensitize to PARP inhibition were randomised to receive olaparib at either 300 mg BID or 400 mg BID tablets. Patients were recruited from 17 UK hospitals (appendix p 2) and molecularly pre-selected based on targeted next-generation sequencing (NGS) of primary or metastatic prostate cancer biopsies. Eligible patients were men aged 18 years or older, with histologically confirmed prostate adenocarcinoma that had developed metastasis and castration-resistance, whose tumours had a putatively pathogenic mutation or homozygous deletion in a DDR gene that could be associated with sensitivity to PARP inhibition. Patients were required to have previously received at least one but no more than two taxane-based chemotherapy regimens, regardless of prior exposure to novel hormonal agents. Other inclusion criteria included: documented prostate cancer progression at trial entry either by prostate-specific antigen (PSA, according to the PCWG2 criteria[14]), and/or radiologically (according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[15] or by bone scan as per PCWG2 criteria); castrate testosterone levels of <50 ng/dL; Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2; adequate organ function (including haemoglobin ≥9g/dL after protocol amendment in March 15, 2018 (previously ≥10g/dL), platelets ≥100x109/L, serum creatinine ≤1.5 x times above institutional range of normal values and albumin >25 g/dl). Patients previously treated with PARP inhibitors, platinum, cyclophosphamide or mitoxantrone were not eligible, as well as patients with known symptomatic brain metastasis or untreated cord compressions. Baseline count for circulating tumour cells (CTC) (CellSearch® system [Menarini

Silicon Biosystems, Inc, Bryn Athin, USA]) had to be ≥5 cells/7.5 ml blood except for patients with radiologically measurable target lesions ≥2cm in diameter on the baseline CT scan. A full list of inclusion/exclusion criteria, as well as the complete study protocol, is available in the appendix (pp 3-4, 20-148).

Patients provided written informed consent before enrolment, both for the NGS pre-screening and treatment stages. The study was approved by the London, Surrey Borders, Research Ethics Committee (REC reference 11/LO/2019), and co-sponsored by The Royal Marsden Hospital and The Institute of Cancer Research (ICR), London, UK. The trial was conducted in accordance with the principles of good clinical practice and overseen by Independent Data Monitoring (IDMC) and Trial Steering (TSC) committees. A Trial Management Group was responsible for the day-to-day running of the trial. The Clinical Trials and Statistics Unit at the ICR (ICR-CTSU) had overall responsibility for trial coordination, monitoring and analysis.

Randomisation and masking

Patients were registered into the trial for NGS pre-screening, and subsequently, eligible patients were randomly allocated (1:1) to olaparib 300mg BID or olaparib 400mg BID. Randomisation was done centrally by the ICR-CTSU via telephone. The allocation sequence was generated centrally by computer-generated minimisation algorithm derived by ICR-CTSU, with CTC count at screening (≥5 or < 5 cells/7.5 ml blood) as a balancing factor. ICR-CTSU staff involved in the randomisation service were not involved in the clinical running of the trial or data collection. Neither participants nor clinicians were blinded to dose allocation.

Procedures

In the pre-screening part of the study, primary and/or metastatic prostate cancer samples were acquired to identify tumours with putatively deleterious DDRga by targeted NGS at the Cancer Biomarkers Laboratory at The ICR. DNA was extracted from formalin-fixed and paraffin embedded (FFPE) tumour blocks using the FFPE Tissue DNA kit (Qiagen). Samples that passed quality control criteria were used for library preparation using a customized panel (Generead DNAseq Mix-n-Match Panel v2; Qiagen) covering 113 genes; libraries were read using a MiSeq Sequencer (Illumina). Expanded details on sample processing, quality check, and bioinformatics pipelines, as well as the panel design, are available in the appendix (pp 5-7).[16] Patients previously known to have germline aberrations were eligible only upon confirmatory tumour NGS testing.

All patients received olaparib at either of the allocated dose levels (300 and 400mgs BID) continuously in 4-week cycles until evidence of radiographic progression, unacceptable toxicity or patient decision to discontinue. Discontinuation due to clinical progression was based on treating clinician decision; discontinuation based solely on a rising PSA in the absence of radiographic or clinical progression was discouraged. Patients treated with 300mg BID were allowed to increase the olaparib dose to 400mg BID at confirmation of disease progression, providing this was considered clinically indicated by the treating physician and the patient had not previously required a dose reduction for management of toxicity.

Clinical assessments, including review of adverse events, performance status, physical examination and routine blood tests (haematology and biochemistry) took place after 2-weeks of starting treatment, and then at the start of every new 4-weekly cycle.

Radiological assessments (CT scan, bone scan) were performed every 12-weeks. CTC counts were measured every cycle for the first 12-weeks, and thereafter every 12-weeks. CTC counts were centrally analysed, and were not made available to the treating physician. PSA assessment was collected every cycle if available, and every 12-weeks as a minimum. Blood samples for correlative biomarker studies were taken on a 4-weekly basis. Repeated tumour biopsies were optional, and pursued when feasible at baseline, after 1-4 weeks on therapy and at the time of progression. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4. Guidelines on drug interruptions or dose reductions for haematological and non-haematological toxicities were implemented as outlined in the protocol (appendix pp 20-148). Up to 42-days of temporary interruption of treatment was allowed prior to mandating permanent discontinuation.

Outcomes

The primary endpoint was confirmed tumour response, defined as a composite of: objective response by RECIST 1.1 (with PCWG2 caveats) and/or PSA decline of ≥50% from baseline and/or conversion of CTC count from ≥5 cells/7.5 ml blood at baseline to <5 cells/7.5 ml[17]. To be considered a response for the primary analysis, at least one of these three tumour response components, confirmed in a second consecutive assessment obtained four or more weeks later, was required.

Protocol-defined secondary endpoints were: radiographic progression-free survival (rPFS), defined as time from randomisation to first evidence of radiographic progression (by RECIST 1.1 or bone scan as per PCWG2 criteria) or death; time to radiographic progression, defined as time from randomisation to first evidence of

radiographic progression; progression-free survival, defined as time from randomisation until radiographic progression, unequivocal clinical progression or death; overall survival (OS), defined as time from randomisation to death by any cause; time to PSA progression, defined as a confirmed ≥25% increase and absolute increase of ≥ 2 ng/mL in PSA above the nadir (PCWG2); duration of PSA response, defined as the time from the first documented ≥50% decline to PSA progression; best percentage change in PSA from baseline whilst on treatment, percentage change in PSA from baseline at 12 weeks (or earlier if discontinued therapy); proportion of patients with CTC conversion; and the safety and tolerability profile of olaparib in men with mCRPC. Pre-specified exploratory endpoints included the evaluation of response in patients who escalated dose to 400mg BID after progression on 300mg BID. A pharmacokinetics sub-study was planned but due to challenges in recruitment it was closed prematurely with no analyses pursued.

Statistical Analysis

Patients were randomised to either 400mg or 300mg BID of olaparib, under a "pick-the-winner" design[18]. Each dose cohort was assessed independently for the primary endpoint. The sample size to demonstrate the minimum desired antitumour activity was based on a one-stage A'Hern design, with RR≤30% for the null hypothesis, and RR>50% for the alternative hypothesis (one-sided alpha level 0.05; beta level 0.15). If at least 19/44 evaluable patients in a dose cohort responded (43%), then the dose cohort would be considered successful. If the 400 mg BID dose cohort was deemed successful, the biomarker identified in TOPARP-A, where all patients received 400mg BID, would be considered validated. In the event of both dose cohorts being successful, the pick-

the-winner selection strategy would include consideration of secondary endpoints. No formal interim analyses were planned.

For the primary endpoint, the evaluable population was defined as all randomised patients who met all of the inclusion and exclusion criteria, and commenced trial treatment, unless they discontinued treatment prior to 12-weeks for reasons that were not drug or disease related. Sensitivity analyses of the primary endpoint on the ITT (all randomised patients) and per protocol (all evaluable patients who received at least one cycle of olaparib, and had no major protocol violations) populations were conducted. A post-hoc sensitivity analysis on patients with CTC count $\geqq$5 cells/7.5ml blood at baseline was performed for comparison with TOPARP-A results. All other efficacy analyses were performed on the ITT population.

Analysis of the primary endpoint was triggered when all patients had completed at least 6-months of treatment (in the absence of prior discontinuation). Evaluable patients who discontinued prior to 12-weeks due to progression or toxicity and had no follow-up assessments for the primary endpoint were considered non-responders. Response rates are presented along with exact two-sided 95% confidence intervals. Local radiological response assessment was used for the primary endpoint definition; all RECIST 1.1 responses were confirmed by central review. Percentage changes from baseline in PSA levels and sum of target lesions, are represented in waterfall plots. Time-to-event endpoints are summarised by Kaplan-Meier curves, and median times estimated with 95% confidence intervals. For rPFS and PFS, patients alive and without progression were censored at the last scheduled disease assessment on study. For time to radiographic progression, patients who did not progress radiologically were censored at

the last scheduled disease assessment on study or date of death, whichever occurred earlier. Patients alive at the end of follow-up were censored for the analysis of OS. Landmark analyses were used to explore the association between CTC conversion at 8- and 12-weeks and rPFS and OS.

Subgroup analysis based on different genes of interest were pre-planned for efficacy endpoints. Five non-mutually exclusive subgroups were predefined: patients with alterations in *BRCA1*/*BRCA2*; *ATM*, *CDK12*, *PALB2*, and, lastly, patients with alterations in any other gene related to DDR or associated to PARPi sensitivity. Patients that had more than one DDRga were included in the analysis of all relevant subgroups.

Toxicity was analysed on all patients who received at least one dose of olaparib, and worst grades of adverse events (AEs) during treatment for each dose cohort are reported. Serious AEs and deaths observed within 30-days of the last dose of study treatment were summarised by dose cohort, as well as the exposure to study drug and reasons for discontinuation, dose modification or interruption and /or treatment delay.

The trial was not powered for head-to-head direct comparisons of the two dose-cohorts, so tests to compare them are considered hypothesis-generating (e.g. Chi-square test to compare response rates, and log-rank test to compare Kaplan-Meier curves). Further exploratory analyses are planned in the protocol and will be reported elsewhere. Statistical analyses were conducted with the use of Stata software (version 15), on a snapshot of the data taken on July 5, 2019. The Statistical Analysis Plan is available in the appendix (pp 149-177)**.**

This study was registered with ClinicalTrials.gov (NCT01682772) and on the European Clinical Trials database (EudraCT 2011-000601-49).

Role of the funding sources

The funders had no role in the study design, data collection, analysis and interpretation, or in the preparation of the report. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

RESULTS

Between April 1 2015 and August 30 2018, 711 patients consented for NGS pre-screening (Figure 1A). For 30 (4.2%) patients, no samples were made available for testing. From 681 patients with at least one sample available, 779 tumour samples were analysed (637 [82%] primary tumour samples, 142 [18%] post-castration resistance metastatic biopsies). For 89 (13%) patients, biomarker determination was not possible due to the sample, or the sequencing data, not fulfilling quality control parameters.

Of the 592 patients with evaluable tissue samples, 161 (27%) had DDRga based on NGS, while 431 (73%) did not. An oncoprint summarizing all alterations detected in the pre-screening phase of the study is presented in the appendix (p 14)**.** The commonest detected DDRga were mutations or homozygous deletions in *BRCA2* (44/592, 7.4%), *ATM* (40/592, 6.8%) and *CDK12* (33/592, 5.6%).

Ninety-eight DDRga patients were randomised and treated in the two dose-level cohorts (49 patients in each cohort). At the time of data snapshot, two patients remained on olaparib treatment. More participants were recruited than originally planned, at the recommendation of the IDMC, to account for six participants (three in each cohort) who were deemed not evaluable (determined ineligible post-randomisation) for the primary endpoint analyses. Median follow-up was 24.8 months (Q1-Q3 16.7 to 35.9 months).

Patients baseline characteristics are shown in Table 1; all had previously received docetaxel, and 88 (90%) had also been treated with abiraterone acetate (46) and/or enzalutamide (56) prior to study entry. The commonest sites for metastases at trial entry were bone (82; 84%) and lymph nodes (66; 67%), with measurable soft-tissue disease

being present in 75 (77%) patients. The distribution of gene subgroups was largely similar between the two dose cohorts, except for *CDK12* alterations which was imbalanced (31% 300mg vs 12% 400mg). The composition of pre-specified gene subgroups per cohort is shown in Figure 1B. Baseline features for each gene subgroup are summarised in the appendix (p 8).

For the 92 patients in the evaluable population for the primary endpoint, 70 (76%), 89 (97%) and 55 (60%) were evaluable for the RECIST 1.1, PSA, and CTC conversion components of the response definition respectively. The confirmed composite response rates were 25/46 (54%; 95%CI 39-69%) in the 400mg cohort, and 18/46 (39%; 95%CI 25-55%) in the 300mg cohort (p-value p=0.14) (Table 2***).*** For each component of the primary endpoint, response rates were: radiological response 400mg 8/33 (24%) vs 300mg 6/37 (16%); PSA response 400mg 17/46 (37%) vs 300mg 13/43 (30%).; CTC count conversion 400mg 15/28 (54%), 300mg 13/27 (48%). Based on the first 44 evaluable patients included in each cohort (as planned initially), there were 25/44 confirmed responses in the 400mg BID cohort, and 18/44 confirmed responses in the 300mg BID cohort; hence, the predefined criteria for success was met for 400mg BID but not for 300mg BID.

When considering only the 55 evaluable patients with $\geq$5 CTC/7.5ml blood at baseline, confirmed composite response rates were 61% (17/28, 95%CI 41-79%) in the 400mg cohort, and 48% (13/27, 95%CI 29-68%) in the 300mg cohort (see appendix p 9 for each individual component). In keeping with previous reports[17,19], CTC conversions post-treatment significantly associated with longer rPFS and OS in landmark analyses (appendix p 15).

Maximum change from baseline in PSA and sum of target lesions while on allocated treatment are presented in Figure 2A and 2B. Overall, 45 ITT patients at 400mg (92%) and 46 ITT patients at 300mg (94%) had radiographic progression or death; median rPFS was 5.5 months (95%CI 4.4-8.3) in the 400mg cohort, and 5.6 months (95%CI 3.7-7.7) in the cohort (Figure 2C). At the time of analyses, 39 400mg (80%) and 38 300mg (78%) patients were deceased, with a median overall survival of 14.3 months (95%CI 9.7-18.9) in the 400mg cohort and 10.1 months (95%CI 9-17.7) in the 300mg cohort. Further results on the secondary endpoints are summarised in the appendix (pp 16-18). Time on treatment for each patient is represented in Figure 2D**.** A summary of treatment dose reductions, interruptions and discontinuations by dose cohort is presented in the appendix (p 10).

Dose escalation from 300 mg to 400 mg was pursued in 11 patients; at the time of the data snapshot, 10 had discontinued treatment: two due to adverse events and eight for disease progression. These 11 patients were on treatment with 400mg for a median of 7.8 weeks (Q1-Q3: 3.7-10.4). None of these patients achieved a response after dose-escalation.

The confirmed composite response rates, and by individual components, for each of the predefined gene subgroups are shown in Table 2**.** Further analysis of secondary endpoints per gene subgroup can be found in Figure 3 and appendix (pp 11, 19).

The *BRCA1/BRCA2* subgroup had the highest response rate (25/30, 83%, 95%CI 65-94%), and the longest median rPFS of all DDRga subgroups (8.3 months, 95%CI 5.5-

13.0). The median OS for the *BRCA1/BRCA2* subgroup was 17.7 months (95%CI 9.9-22.2). Of the 32 patients included in this *BRCA1/BRCA2* subgroup, 13 had germline mutations in *BRCA2*, six somatic mutations in *BRCA2*, 11 homozygous deletions in *BRCA2*, and the remaining two cases had mutations in *BRCA1* (one germline, one somatic). Ten patients in the *BRCA1/BRCA2* subgroup (five allocated to 400mg BID, five allocated to 300mg BID) remained on treatment for over one year.

Twenty-one patients with suspected deleterious *ATM* aberrations were treated (one patient with homozygous deletion; the rest with germline or somatic mutations that are predicted to either result in truncation or missense mutations affecting the kinase domain). The composite response rate in patients with *ATM* aberrations was 37% (7/19; 95%CI 16-62%), with only 2 of those were RECIST/PSA responses (appendix p 12). Median rPFS and OS for the *ATM* altered subgroup were 5.8 months (95%CI 4.4-10.9) and 16.6 months (95%CI 8.9-24.2), respectively.

No confirmed PSA or RECIST responses were observed in the *CDK12* mutated subgroup, although 5/12 evaluable patients achieved a CTC conversion (including one with concomitant *BRCA1/2* alteration) (appendix pp 13). Median rPFS was 2.9 months (95% CI 2.6-7.5) and median OS was 9.5 months (95%CI 8.2-10.1).

Conversely, 4/7 (57%; 95%CI 18-90%) patients with *PALB2* mutations responded to treatment, all four had confirmed PSA responses, and two of them also had confirmed radiological responses. The median rPFS and OS in this subgroup were 5.3 months and 13.9 months respectively (95% CI could not be estimated due to small number of patients/events).

Lastly, 21 patients were evaluated as part of the subgroup with "other gene alterations". The composite response rate in this subgroup was 20% (4/20 patients, 95%CI 6-44), with median rPFS of 2.8 months (95%CI 2.6-4.3) and median OS of 7.7 months (95%CI 4.3-19.1). PSA responses were seen in one patient whose tumour had a somatic nonsense mutation in *FANCA* and one patient with a *CHEK2* mutation.

The safety population included all 98 patients treated. The tolerability profile was in line with what has been previously reported for olaparib and other PARP inhibitors[20-22] (Table 3). Anaemia was the most common treatment-emergent adverse event (69%), with 34% experiencing G3-4 anaemia. Fatigue was also common (54.1%; 7% grade 3-4). Grade 3-4 gastrointestinal toxicities were rare (1% nausea, 2% decreased appetite, 2% diarrhoea). Anaemia was the commonest AE leading to dose reductions; 18 (37%) patients in the 400mg cohort, and six (12%) in the 300mg cohort, required at least one dose reduction (appendix p 10). Eight patients achieving a response while on 400mg, continued to respond for more than 6-months after dose reduction to 300mg or lower. Overall, 18/98 (19%) patients were permanently discontinued from olaparib treatment due to AE.

A total of 107 serious adverse events were reported in 49 (50%) patients, with 19 serious adverse reactions (SAR, possibly related to study drug, 11 in 300mg, 8 in 400mg) in 13 patients. The commonest SAR was anaemia (6 in 300mg, 5 in 400mg). Four SAR were considered suspected unexpected (SUSAR, two in each dose cohort group), including a patient diagnosed with myelodysplasia after 6.5 months of 300mg olaparib. This patient developed acute myeloid leukaemia after olaparib discontinuation.

One 300mg patient (2%) died due to a myocardial infarction, assessed as possibly drug related, after 11-days of treatment. All other deaths were unrelated to treatment.

DISCUSSION

TOPARP-B has confirmed the antitumour activity of olaparib against metastatic prostate cancers (mPC) with specific DDRga. The number of composite responses observed in the 400mg BID cohort met the predefined criteria for success, validating the biomarker identified in TOPARP-A[12]. Overall, the data suggest that both drug dose and the specific DDR gene aberration type may matter to antitumour activity since the composite response rate at the 300mg BID was lower and did not reach predefined criteria for success. The antitumour activity observed varied considerably for different DDRga, with the most impressive antitumour activity seen in the *BRCA1/BRCA2*-altered subgroup.

Despite randomisation, there was an imbalance in *CDK12* aberrations between cohorts, with an enrichment for these in the 300mg cohort. This may explain, at least in part, the inferior composite response rate in the 300mg cohort[4,23]. The rationale to explore these two dose levels originated from prior clinical observations indicating a dose-response relationship for olaparib between 100mg BID and 400mg BID, although this dose increase is associated with increased toxicity [24,25]. In keeping with this, 37% patients at 400mg BID had to dose reduce to 300mg BID, most commonly due to anaemia; all these data would need to be considered when assessing the optimal dose of olaparib for prostate cancer care.

These results support the implementation of routine genomic testing of metastatic prostate cancer, to detect DNA repair defects for PARP inhibition. In previous studies, we reported an enrichment for germline inherited mutations in DDR genes in this mCRPC population[26], which has led to a recommendation of broad germline NGS

testing for all men suffering from mPC per NCCN guidelines. The antitumour activity demonstrated herein for olaparib in mCRPC patients with both germline and somatic aberrations of *BRCA2* now supports the implementation of NGS testing of tumour samples.

Antitumour activity was also observed in other DDRga subgroups. Responses in tumours with *PALB2* mutations were frequent (4/7 patients), although the low prevalence of these mutations means that further data are required to confirm these findings. Clinical qualification of low-prevalence biomarkers is challenging in the pursuit of precision medicine approaches; the validation of genomic signatures[23,27] or functional biomarkers[28] that identify tumours with defective homologous-recombination, regardless of the mutated gene of origin, could help move the field forward, but such assays have not been yet validated in prostate cancer.

Conversely, germline and somatic *ATM* aberrations are common in mPC; *ATM* functions as a cell cycle checkpoint, preventing cell cycle progression in the presence of DNA damage rather than directly mediating repair unlike *BRCA2* and *PALB2*. In the TOPARP-A trial, 5 patients had *ATM* aberrations in tumour biopsies: 2 of these had a PSA response, and a further 2 achieved a CTC conversion. Preliminary reports suggest that rucaparib, another PARP inhibitor, resulted in few PSA falls in patients with *ATM* aberrations[29]. In TOPARP-B, we treated 21 patients with suspected deleterious *ATM* aberrations; two of them achieved a RECIST/PSA response, and several others had CTC counts conversions following therapy. CTC count falls seen in this sub-group associated with longer duration on trial, tumour shrinkage by RECIST and PSA falls (appendix p 12), as was the case for the overall TOPARP-B population, with CTC

conversions robustly associating with longer rPFS and OS. Overall, these data indicate that the antitumour activity of olaparib in *ATM* loss mCRPC is less than that for *BRCA* altered tumours; nevertheless, a subset of these patients with *ATM* altered mCRPC appear to derive benefit. Detection of *ATM* alterations alone may, however, be insufficient to identify these sensitive tumours. Further studies, as well as the study of rational drug combinations, are now needed to elucidate how to best evaluate and treat mCRPC with *ATM* alterations. Ongoing exploratory analysis from this trial will look into further characterization of exceptional responses within each gene-defined subgroup to optimize patient stratification.

We do acknowledge limitations to this study. While the utilization of targeted NGS facilitates the clinical implementation of patient stratification, this may be insufficient to capture more complex aberrations resulting in PARPi sensitivity. Moreover, as all patients in this study had DDRga and received olaparib, we are not able to fully differentiate the predictive value versus the prognostic impact on of the survival data. Randomised trials including biomarker-positive and biomarker-negative patients are more able to clinically qualify a putative predictive biomarker.

Nonetheless, these TOPARP results have overall driven the design and conduct of multiple registration trials of PARP inhibitors in mCRPC that are likely to guide the clinical use of PARP inhibitors in mPC in the future. Most of these studies aim to validate PARP inhibition as a precision medicine strategy for prostate cancers with DDRga; other studies, in parallel, explore the addition of PARP inhibitors to standard-of-care AR targeting agents, based on results from a phase II clinical trial which has

been reported to indicate that a broader target population may benefit from these agents[30].

In conclusion, these TOPARP-B data have confirmed the antitumour activity of olaparib against mPC with certain DDRga. The high response rates observed in patients with mCRPC with germline or somatic *BRCA1/2* aberrations, and the durability of many of these responses, support the use of olaparib in this sub-population. The antitumour activity observed against tumours with *ATM, PALB2*, *FANCA* or *CHEK2* aberrations suggest that PARPi may have a role as a single agent or in rational combinations against these other mPC subtypes, although further data are needed to precisely assess the clinical relevance of each of these different DDRga in prostate cancer.

Figure legends

Figure 1. (A) CONSORT Flow diagram of patient disposition in the TOPARP-B trial (B) Oncoprint of mutations and homozygous deletions in DDR genes that led to trial inclusion for the IIT population (n=98)**.

DDRga= Defective DNA Repair Gene aberration

** Non-mutually exclusive subgroups: One patient treated at 300mgs BID had BRCA1/2, CDK12 & 'Other mutations' (300mg); two further 300 mg patients had both PALB2 & 'Other mutations'.*

*** The BRCA2 K3226* variant was not considered sufficient for patients to be considered eligible; however, one patient with a BRCA2 K3226* variant was included due to evidence of concomitant loss of the contralateral allele.*

Figure 2. Antitumour activity by allocated dose cohort (IIT population): (A) Best percentage change from baseline in PSA whilst on allocated treatment; (B) Best percentage change from baseline in sum of target lesions (RECIST 1.1) whilst on allocated treatment; (C) Radiographic Progression-Free Survival; (D) Swimmers plot of time on treatment for each patient, indicating periods of treatment interruptions, dose reductions or dose-escalations (in the 300mg dose cohort).

Figure 3. Antitumour activity by gene subgroup (IIT population, pooled 300mg and 400mg BID cohorts): (A) Best percentage change from baseline in PSA whilst on allocated treatment; (B) Best percentage change from baseline in sum of target lesions (RECIST 1.1) whilst on allocated treatment; (C) Radiographic Progression-Free Survival; (D) Swimmers plot of time on treatment for each patient.

(*) indicate patients with different mutations qualifying for more than one subgroup.

Table 1. Baseline characteristics of TOPARP-B patients in the ITT population, presented by dose cohort

	Total (N=98)		**Dose group**			
			300 mg (N=49)		**400 mg (N=49)**	
Age at trial entry, mean (SD)	67.6 (7.6)		67.7 (7.4)		67.4 (7.8)	
Years from initial diagnosis - median (Q1-Q3)	4.6 (2.8-7)		3.5 (2.4-6.4)		5.2 (3.6-7.3)	
Years from diagnosis of CRPC - median (Q1-Q3)	2.6 (1.6-4)		2.4 (1.2-3.7)		3.0 (1.8-4)	
Metastatic disease at diagnosis, n (%)						
Yes	49	(50%)	24	(49%)	25	(51%)
No	45	(45.9%)	24	(49%)	21	(42.9%)
Not available	4	(4.1%)	1	(2%)	3	(6.1%)
Gleason score at diagnosis, n (%)						
≤7	19	(19.4%)	4	(8.2%)	15	(30.6%)
≥8	71	(72.4%)	42	(85.7%)	29	(59.2%)
Not available	8	(8.2%)	3	(6.1%)	5	(10.2%)
Previous treatment for PC, n (%)						
Prostatectomy	13	(13.3%)	7	(14.3%)	6	(12.2%)
Radical radiotherapy	43	(43.9%)	22	(44.9%)	21	(42.9%)
Biphosphonates	4	(4.1%)	2	(4.1%)	2	(4.1%)
Radium 223	*14*	*(14.3%)*	*6*	*(12.2%)*	*8*	*(16.3%)*
Docetaxel	98	(100%)	49	(100%)	49	(100%)
Cabazitaxel	37	(37.8%)	15	(30.6%)	22	(44.9%)
Abiraterone	46	(46.9%)	24	(49%)	22	(44.9%)
Enzalutamide	56	(57.1%)	27	(55.1%)	29	(59.2%)
Abiraterone and/or Enzalutamide	88	(89.8%)	43	(87.8%)	45	(91.8%)
Evidence of progression at trial entry, n (%)						
PSA only	27	(27.6%)	15	(30.6%)	12	(24.5%)
Radiographic progression (+/- PSA progression)	71	(72.4%)	34	(69.4%)	37	(75.5%)
Site of metastatic disease at trial entry, n (%) [(1)]						
Lung	8	(8.2%)	4	(8.2%)	4	(8.2%)
Lymph nodes	66	(67.3%)	34	(69.4%)	32	(65.3%)
Liver	23	(23.5%)	11	(22.4%)	12	(24.5%)
Bone	82	(83.7%)	41	(83.7%)	41	(83.7%)
PSA at trial entry (ng/ml) – median (Q1-Q3)	154.8 (45.5-472.0)		151.5 (49.0-446.0)		158.0 (45.5-472.0)	
CTC count at trial entry, n (%)	**n**	**%**	**n**	**%**	**n**	**%**
CTC<5	34	(34.7%)	17	(34.7%)	17	(34.7%)

	Total (N=98)		Dose group			
			300 mg (N=49)		400 mg (N=49)	
CTC >= 5	63	(64.3%)	31	(63.3%)	32	(65.3%)
Not available [2]	1	(1%)	1	(2%)	0	(0%)
RECIST soft tissue disease, n (%)						
Bone lesions only	10	(10.2%)	5	(10.2%)	5	(10.2%)
Non-measurable disease only (+/- bone lesions)	13	(13.3%)	5	(10.2%)	8	(16.3%)
Measurable disease (+/- bone lesions)	75	(76.5%)	39	(79.6%)	36	(73.5%)
DDRga gene subgroup, n (%)[3]	**n**	**%**	**n**	**%**	**n**	**%**
BRCA1/2	32	(32.7%)	15	(30.6%)	17	(34.7%)
ATM	21	(21.4%)	10	(20.4%)	11	(22.5%)
CDK12	21	(21.4%)	15	(30.6%)	6	(12.4%)
PALB2	7	(7.1%)	3	(6.1%)	4	(8.2%)
Other	21	(21.4%)	10	(20.4%)	11	(22.5%)

Q1: 25% percentile, Q3: 75% percentile

(1) More than one site could be reported.

(2) Screening CTC assessment not possible due to CTC kit shortage. Patient allowed to be randomised as he had RECIST 1.1 measurable disease; for randomisation CTC assumed <5 but patient was unevaluable for CTC response.

(3) Non-mutually exclusive subgroups: one 300mg cohort patient had *BRCA1/2, CDK12* and 'Other mutations', and two 300 mg cohort patients with *PALB2* mutations also had other mutations (in *MSH2* and *NBN* respectively).

Table 2. Overall antitumour activity in patients with DDRga, by dose cohort and by gene subgroup (evaluable population; confirmed responses)

	Composite overall response			RECIST 1.1 Objective Response			PSA fall ≥50%			CTC conversion			RECIST 1.1 or PSA response		
	resp/n	**RR**	**95% CI**	**resp/n**	**%**	**95% CI**	**resp/n**	**%**	**95% CI**	**resp/n**	**%**	**95% CI**	**resp/n**	**%**	**95% CI**
Evaluable patients	**43/92**	**46.7**	**36.3-57.4**	**14/70**	**20.0%**	**11.4-31.3**	**30/89**	**33.7%**	**24.0-44.5**	**28/55**	**50.9%**	**37.1-64.6**	***32/92***	***34.8%***	***25.1-45.4***
By dose cohort:															
300 mg BID	18/46	39.1	25.1-54.6	6/37	16.2%	6.2-32.0	13/43	30.2%	17.2-46.1	13/27	48.1%	28.7-68.1	*13/46*	*28.3%*	*16.0-43.5*
400 mg BID	25/46	54.3	39.0-69.1	8/33	24.2%	11.1-42.3	17/46	37.0%	23.2-52.5	15/28	53.6%	33.9-72.5	*19/46*	*41.3%*	*27.0-56.8*
By gene subgroup[¥]															
BRCA 1/2	25/30	83.3	65.3-94.4	11/21	52.4%	29.8-74.3	23/30	76.7%	57.7-90.1	17/22	77.3%	54.6-92.2	24/30	80.0%	61.4-92.3
ATM	7/19	36.8	16.3-61.6	1/12	8.3%	0.2-38.5	1/19	5.3%	0.1-26.0	5/10	50.0%	18.7-81.3	2/19	10.5%	1.3-33.1
CDK12	5/20	25.0	8.7-49.1	0/18	0.0%	0-18.5*	0/20	0.0%	0-16.8*	5/12	41.7%	15.2-72.3	0/20	0.0%	0-16.8*
PALB2	4/7	57.1	18.4-90.1	2/6	33.3%	4.3-77.7	4/6	66.7%	22.3-95.7	0/2	0.0%	0-84.2*	4/7	57.1%	18.4-90.1
Other	4/20	20.0	5.7-43.7	0/17	0.0%	0-19.5*	2/17	11.8%	1.5-36.4	3/11	27.3%	6.0-61.0	2/20	10.0%	1.2-31.7

Resp/n: number of observed responses / number of evaluable patients; RR: response rate, 95% CI: 95% confidence interval. *One-sided exact binomial 95% confidence intervals

[¥]Non-mutually exclusive subgroups: One patient treated at 300mgs BID had *BRCA1/2*, *CDK12* & 'Other mutations' (300mg); two further 300 mg patients had both *PALB2* & 'Other mutations'. These patients have been included in analysis for each subgroup separately. For the gene subgroup analyses, dose cohorts have been pooled.

Table 3 – Treatment emergent adverse events, by dose cohort

Any grade 1-2 event occurring in ≥10% of patients is reported. All grade 3, 4, and 5 events are reported.

*Includes one G5 event (myocardial infarction), grouped with G4 for conciseness.

	300mg (N=49)			400mg (N=49)		
MedDRA preferred term	**G2**	**G3**	**G4***	**G2**	**G3**	**G4**
Anaemia	16 (32.7)	14 (28.6)	1 (2.0)	19 (38.8)	18 (36.7)	0
Fatigue	19 (38.8)	3 (6.1)	0	27 (55.1)	4 (8.2)	0
Back pain	13 (26.5)	4 (8.2)	0	11 (22.4)	3 (6.1)	0
Nausea	17 (34.7)	1 (2.0)	0	13 (26.5)	0	0
Platelet count decreased	9 (18.4)	2 (4.1)	1 (2.0)	12 (24.5)	3 (6.1)	0
Decreased appetite	13 (26.5)	2 (4.1)	0	10 (20.4)	0	0
Vomiting	10 (20.4)	0	0	15 (30.6)	0	0
Weight decreased	9 (18.4)	1 (2.0)	0	15 (30.6)	0	0
Diarrhoea	8 (16.3)	1 (2.0)	0	10 (20.4)	1 (2.0)	0
Arthralgia	8 (16.3)	1 (2.0)	0	5 (10.2)	4 (8.2)	0
Hypertension	9 (18.4)	1 (2.0)	0	4 (8.2)	4 (8.2)	0
Neutrophil count decreased	9 (18.4)	2 (4.1)	0	4 (8.2)	2 (4.1)	1 (2.0)
Dyspnoea	5 (10.2)	1 (2.0)	0	10 (20.4)	1 (2.0)	0
Abdominal pain	4 (8.2)	0	0	6 (12.2)	5 (10.2)	1 (2.0)
Blood creatinine increased	9 (18.4)	0	0	6 (12.2)	0	0
Oedema peripheral	6 (12.2)	0	0	8 (16.3)	1 (2.0)	0
Urinary tract infection	3 (6.1)	3 (6.1)	0	6 (12.2)	3 (6.1)	0
Constipation	7 (14.3)	0	0	7 (14.3)	0	0
Cough	3 (6.1)	0	0	9 (18.4)	0	0
Musculoskeletal chest pain	3 (6.1)	0	0	9 (18.4)	0	0
Musculoskeletal pain	5 (10.2)	1 (2.0)	0	5 (10.2)	1 (2.0)	0
Hypokalaemia	3 (6.1)	0	0	8 (16.3)	0	0
Muscular weakness	4 (8.2)	0	0	5 (10.2)	2 (4.1)	0
WBC count decreased	4 (8.2)	0	0	6 (12.2)	1 (2.0)	0
AST increased	3 (6.1)	0	1 (2.0)	4 (8.2)	1 (2.0)	0
ALP increased	3 (6.1)	0	0	5 (10.2)	1 (2.0)	0
Dysgeusia	6 (12.2)	0	0	3 (6.1)	0	0
Haematuria	5 (10.2)	0	0	2 (4.1)	2 (4.1)	0
Influenza like illness	3 (6.1)	0	0	6 (12.2)	0	0
Muscle spasms	3 (6.1)	0	0	6 (12.2)	0	0

	300mg (N=49)			400mg (N=49)		
MedDRA preferred term	**G2**	**G3**	**G4***	**G2**	**G3**	**G4**
GGT increased	3 (6.1)	0	0	2 (4.1)	2 (4.1)	1 (2.0)
Lower resp. tract infection	4 (8.2)	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Lymphocyte count decreased	2 (4.1)	1 (2.0)	0	3 (6.1)	2 (4.1)	0
Pyrexia	4 (8.2)	2 (4.1)	0	2 (4.1)	0	0
ALT increased	2 (4.1)	0	0	3 (6.1)	2 (4.1)	0
Groin pain	3 (6.1)	0	0	2 (4.1)	2 (4.1)	0
Dizziness	2 (4.1)	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Spinal cord compression	0	1 (2.0)	0	0	5 (10.2)	0
Blood bilirubin increased	1 (2.0)	0	0	3 (6.1)	0	1 (2.0)
Cellulitis	2 (4.1)	0	0	2 (4.1)	1 (2.0)	0
Pain	1 (2.0)	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Hydronephrosis	1 (2.0)	2 (4.1)	0	0	1 (2.0)	0
Hyponatraemia	0	1 (2.0)	0	2 (4.1)	1 (2.0)	0
Myocardial infarction	0	1 (2.0)	**2 (4.1)***	0	1 (2.0)	0
Acute kidney injury	1 (2.0)	0	1 (2.0)	1 (2.0)	0	0
Hyperkalaemia	0	1 (2.0)	0	2 (4.1)	0	0
Rectal haemorrhage	0	1 (2.0)	0	1 (2.0)	1 (2.0)	0
Amylase increased	0	0	0	1 (2.0)	1 (2.0)	0
Atrial fibrillation	0	0	0	1 (2.0)	1 (2.0)	0
Circulatory collapse	0	2 (4.1)	0	0	0	0
Confusional state	1 (2.0)	1 (2.0)	0	0	0	0
Femoral neck fracture	0	1 (2.0)	0	1 (2.0)	0	0
Femur fracture	0	0	0	0	2 (4.1)	0
Mobility decreased	1 (2.0)	0	0	0	1 (2.0)	0
Pneumonia	0	0	0	0	2 (4.1)	0
Presyncope	1 (2.0)	0	0	0	1 (2.0)	0
Pulmonary embolism	0	1 (2.0)	0	0	1 (2.0)	0
Respiratory tract infection	1 (2.0)	1 (2.0)	0	0	0	0
Abdominal infection	0	1 (2.0)	0	0	0	0
Acute myeloid leukaemia	0	0	1 (2.0)	0	0	0
Arthritis bacterial	0	1 (2.0)	0	0	0	0
Bronchitis	0	1 (2.0)	0	0	0	0
Cauda equina syndrome	0	0	0	0	1 (2.0)	0
Embolism	0	0	0	0	1 (2.0)	0
Enterocolitis infectious	0	0	0	0	1 (2.0)	0
Febrile neutropenia	0	0	0	0	1 (2.0)	0
Hip fracture	0	1 (2.0)	0	0	0	0
Intestinal obstruction	0	0	0	0	1 (2.0)	0

	300mg (N=49)			400mg (N=49)		
MedDRA preferred term	**G2**	**G3**	**G4***	**G2**	**G3**	**G4**
Jaundice	0	0	0	0	1 (2.0)	0
Neutropenic sepsis	0	0	0	0	1 (2.0)	0
Pyelonephritis	0	0	0	0	1 (2.0)	0
Radiculopathy	0	0	0	0	1 (2.0)	0
Renal colic	0	1 (2.0)	0	0	0	0
Sepsis	0	0	0	0	0	1 (2.0)
Ureteric obstruction	0	1 (2.0)	0	0	0	0
Urosepsis	0	1 (2.0)	0	0	0	0
Vascular pseudoaneurysm	0	0	1 (2.0)	0	0	0
Vision blurred	0	1 (2.0)	0	0	0	0

RESEARCH IN CONTEXT

Evidence before this study

Trials for advanced prostate cancer have rarely pursued molecular stratification, and none of the drugs approved up to date for metastatic prostate cancer care have a validated companion biomarker. Before starting this study, several genomic landscape studies were published describing an enrichment for aberrations in DNA repair genes in metastatic prostate cancers (studies identified in Pubmed, searching for "prostate cancer", "genomics", "biopsy", between 2010 and 2015). Preclinical and clinical studies identified in Pubmed (search for "cancer", "PARP" and "BRCA" or "DNA repair" between 2005 and 2019) have established a correlation between different DNA repair defects and sensitivity to PARP inhibition in different tumour types, leading to drug approvals in ovarian and breast cancer. In the TOPARP-A trial, we identified an association between somatic alterations in DNA repair genes and antitumour activity of olaparib in 49 patients with metastatic prostate cancer. Other clinical trials of PARP inhibitors in prostate cancer were identified using ClinicalTrials.gov website, searching for "prostate cancer" and "PARP".

Added value of this study

To our knowledge, this is the first ever prospective clinical trial for a genomically-defined population of metastatic prostate cancers. TOPARP-B aims to clinically qualify, for the first time, a predictive biomarker for treating metastatic prostate cancers. TOPARP-B also assessed different doses of olaparib, and correlated different genomic aberrations and antitumour activity. This study has confirmed the antitumour activity of olaparib against metastatic prostate cancer with defective DNA repair, secondary to either germline or somatic gene inactivation.

Implications of all the available evidence

Randomised phase III trials for DNA repair defective prostate cancers are now ongoing based on these data. Our results, if confirmed in registration studies, would support implementing tumour genomic testing in clinical practice for treatment stratification in advanced prostate cancer.

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Data sharing statement

The ICR-CTSU supports the wider dissemination of information from the research it conducts, and increased cooperation between investigators. Trial data is collected, managed, stored, shared and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and Intellectual Property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee as required.

Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymizing identifiable patient data. Additionally all indirect identifiers that may lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines.

AUTHOR CONTRIBUTIONS

JM – trial design, protocol development, data collection, participant recruitment, translational experiments, data interpretation, writing, Trial Management Group member; NP – trial design, protocol development, statistical analysis, data interpretation, writing, Trial Management Group member. DB – participant recruitment, data collection. UMG - participant recruitment, data collection, Trial Management Group member. TE - participant recruitment, data collection, Trial Management Group member. RJ – protocol development, participant recruitment, data collection, Trial Management Group member .IS- participant recruitment, data collection, Trial Management Group member. CR - participant recruitment, data collection, Trial Management Group member. SJ - participant recruitment, data collection, Trial Management Group member. MV - participant recruitment, data collection, Trial Management Group member. OP - participant recruitment, data collection, Trial Management Group member. SCr- participant recruitment, data collection, Trial Management Group member. AR - participant recruitment, data collection, Trial Management Group member. DML - participant recruitment, data collection, Trial Management Group member. AB - participant recruitment, data collection, Trial Management Group member .JT - participant recruitment, data collection. SM –data collection, sample processing, translational experiments, data analyses, Trial Management Group member. IF – data collection, sample processing, translational experiments, data analyses. GS –translational experiments, data interpretation, data analyses. CB - data collection, sample processing, translational experiments. PF – protocol development, data collection, data interpretation, data analyses. BE – data collection, sample processing, translational experiments. PR – patient recruitment, data collection. GF – data collection, sample processing, translational experiments. AF –

data collection, sample processing, translational experiments. RP – data collection, sample processing, translational experiments. AC – data collection, data interpretation. RC – patient recruitment, data collection. MCl –translational experiments, data interpretation, data analyses. BG –translational experiments, data interpretation, data analyses. MCr –translational experiments, data interpretation. DNR –translational experiments, data interpretation, data analyses. NT – data collection, data interpretation. AE - trial management, data management, Trial Management Group member. PC - trial management, data management, Trial Management Group member. SS – trial design, protocol development. WY –translational experiments, data interpretation, data analyses EH – trial design, protocol development, statistical analysis, data interpretation, writing, Trial Management Group member. SCa – protocol development, data collection, translational experiments, data analysis, data interpretation, writing. JdB - Chief Investigator, trial design, protocol development, participant recruitment, translational experiments, data collection, data interpretation, writing, Trial Management Group member

All authors reviewed the manuscript prior to submission.

Declaration of Interests

Dr. Mateo reports grants from AstraZeneca, during the conduct of the study; personal fees and non-financial support from AstraZeneca, personal fees from Janssen, personal fees from Amgen, from Roche, outside the submitted work.

Dr. Elliott reports grants from Janssen conference educational grant, grants from Janssen conference educational grant, outside the submitted work.

Prof. Jones reports grants and personal fees from Astellas, grants and personal fees from AstraZeneca, personal fees and non-financial support from Bristol Myers Squibb, grants, personal fees and non-financial support from Bayer, grants and personal fees from Exelixis, personal fees and non-financial support from Janssen, personal fees and non-financial support from Ipsen, personal fees from Merck Serono, personal fees and non-financial support from MSD, personal fees from Novartis, personal fees from Pfizer, grants and personal fees from Roche, personal fees from Sanofi Genzyme, personal fees from EUSA, outside the submitted work .

Dr. Ralph reports non-financial support from Pfizer, non-financial support from Ipsen, personal fees and non-financial support from BMS, personal fees and non-financial support from Eisai, outside the submitted work.

Dr. Jain reports personal fees from Astellas, personal fees from Janssen, personal fees from Bayer, personal fees from Boston Scientific, personal fees from Movember, personal fees from Almac Diagnostics, outside the submitted work.

Dr. Varughese reports non-financial support from Janssen, non-financial support from MSD, outside the submitted work.

Dr. Crabb reports personal fees from Bayer, personal fees from Janssen Cilag, grants from AstraZeneca, grants from Clovis Oncology, grants from Roche, grants from Astex Pharmaceuticals, outside the submitted work.

Dr. Birtle reports other from Sanofi Aventis, other from Astellas, other from Janssen, other from Bayer, other from MSD, other from Roche, from null, outside the submitted work.

Mr. Chatfield reports grants from AstraZeneca, during the conduct of the study.

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Prof. de Bono reports grants from AstraZeneca, during the conduct of the study; personal fees and non-financial support from Astellas Pharma, grants, personal fees and non-financial support from AstraZeneca, personal fees from Genentech/Roche, personal fees from Pfizer, personal fees and non-financial support from Sanofi, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Merck Serono, personal fees from Merck Sharp & Dohme, non-financial support from Genmab, non-financial support from GlaxoSmithKline, non-financial support from Orion Pharma GmbH, non-financial support from Qiagen, non-financial support from Taiho Pharmaceutical, non-financial support from Vertex, personal fees and non-financial support from Menarini/Silicon Biosystems, grants, personal fees and non-financial support from Daiichi , grants, personal fees and non-financial support from

Sierra Oncology, grants, personal fees and non-financial support from Cellcentric, outside the submitted work; In addition, Dr. de Bono has a patent Abiraterone Rewards to Inventors with royalties paid, and a patent PARP inhibitors and DNA repair defects with royalties paid.

The authors affiliated to The Institute of Cancer Research disclose that the institution is joint applicant for the patent entitled 'DNA damage repair inhibitors for treatment of cancer' which includes the granted application US8143241.

All other authors do not declare any potentially relevant conflict of interest.

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Figure 1A

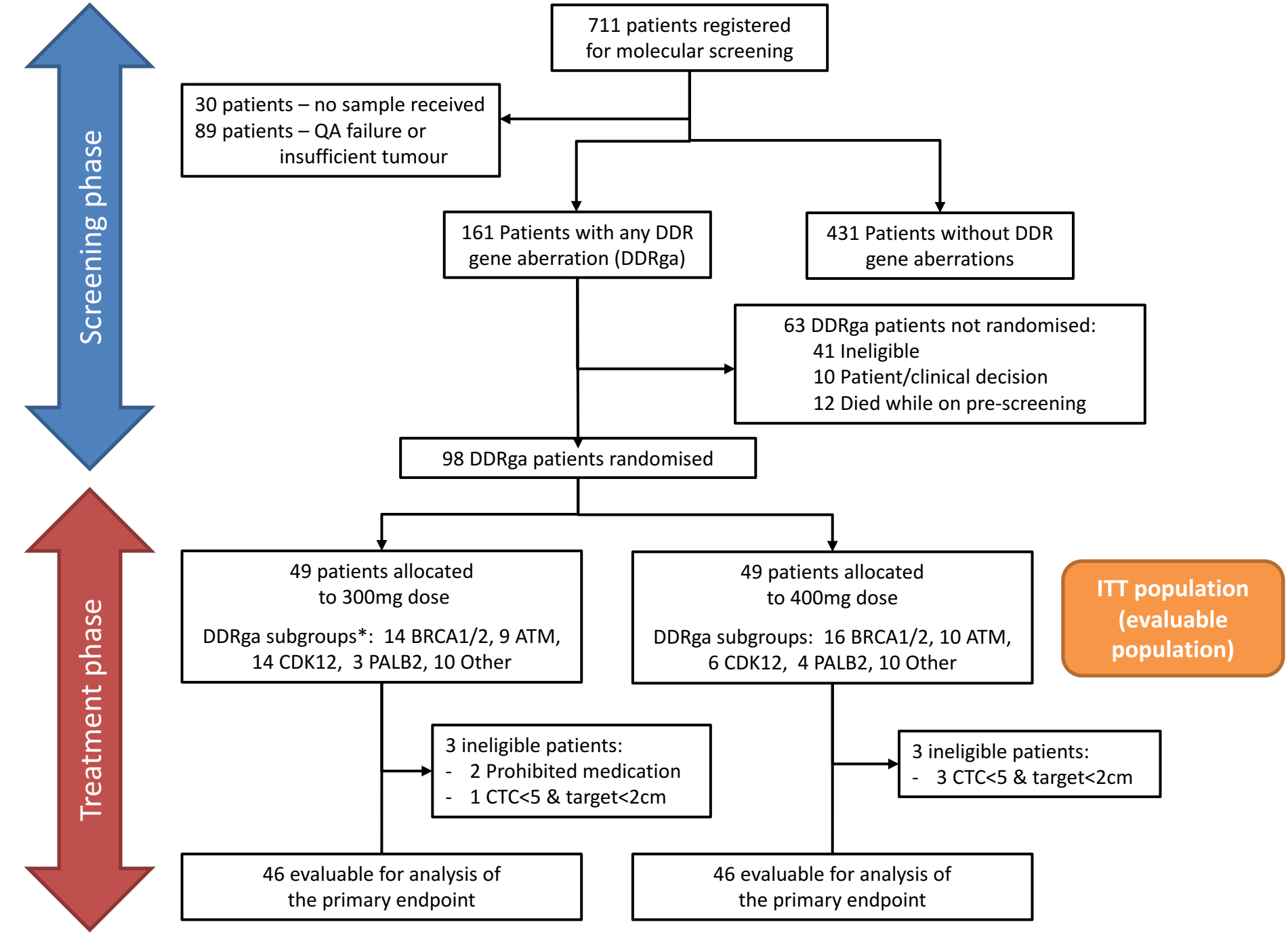

Screening phase
711 patients registered for molecular screening
30 patients – no sample received
89 patients – QA failure or insufficient tumour
161 Patients with any DDR gene aberration (DDRga)
431 Patients without DDR gene aberrations
63 DDRga patients not randomised:
41 Ineligible
10 Patient/clinical decision
12 Died while on pre-screening
98 DDRga patients randomised
Treatment phase
49 patients allocated to 300mg dose
DDRga subgroups*: 14 BRCA1/2, 9 ATM, 14 CDK12, 3 PALB2, 10 Other
49 patients allocated to 400mg dose
DDRga subgroups: 16 BRCA1/2, 10 ATM, 6 CDK12, 4 PALB2, 10 Other
ITT population (evaluable population)
3 ineligible patients:
- 2 Prohibited medication
- 1 CTC<5 & target<2cm
3 ineligible patients:
- 3 CTC<5 & target<2cm
46 evaluable for analysis of the primary endpoint
46 evaluable for analysis of the primary endpoint

Figure 1B

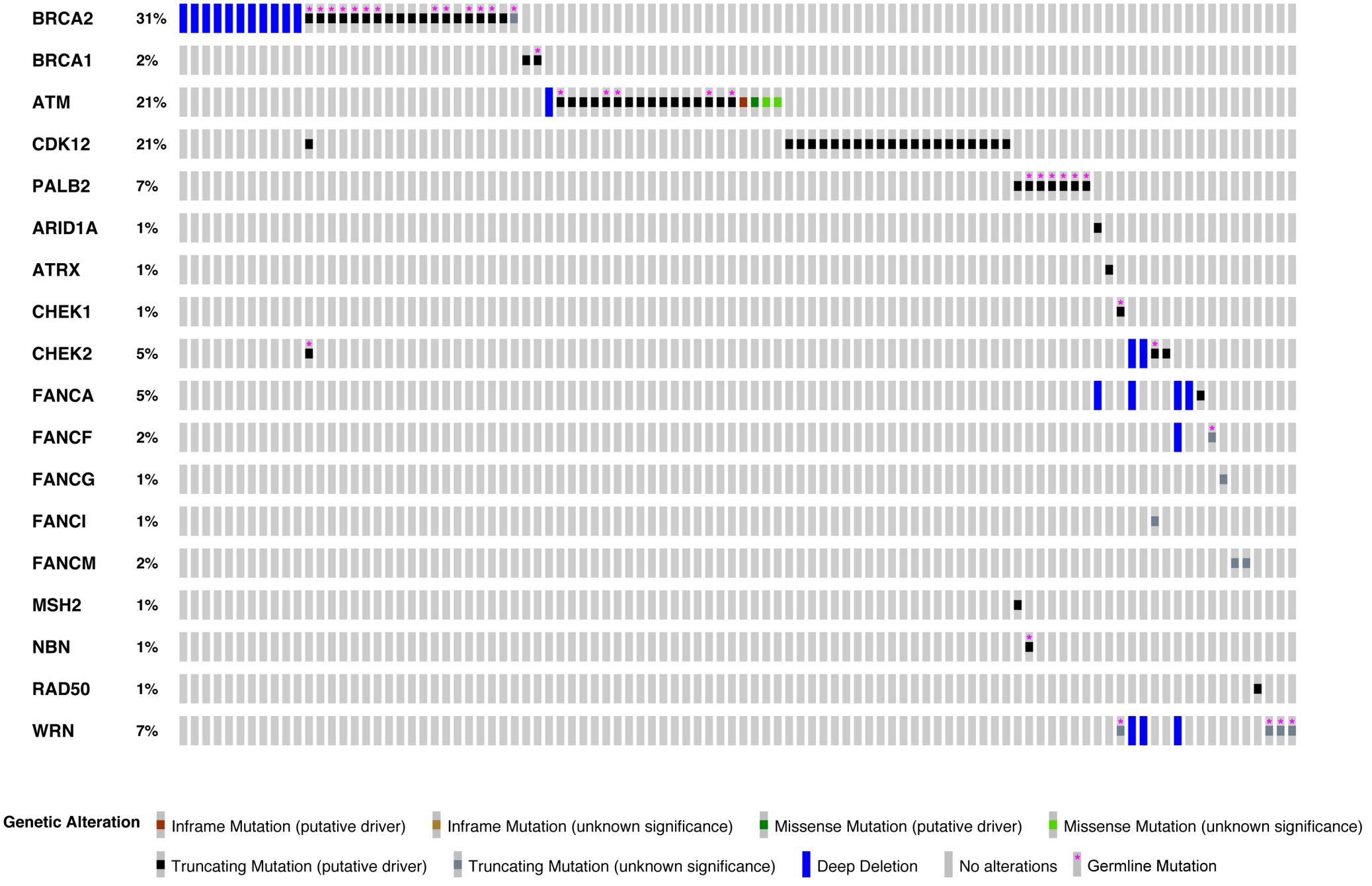

BRCA2 31%
BRCA1 2%
ATM 21%
CDK12 21%
PALB2 7%
ARID1A 1%
ATRX 1%
CHEK1 1%
CHEK2 5%
FANCA 5%
FANCF 2%
FANCG 1%
FANCI 1%
FANCM 2%
MSH2 1%
NBN 1%
RAD50 1%
WRN 7%
Genetic Alteration
Inframe Mutation (putative driver)
Inframe Mutation (unknown significance)
Missense Mutation (putative driver)
Missense Mutation (unknown significance)
Truncating Mutation (putative driver)
Truncating Mutation (unknown significance)
Deep Deletion
No alterations
Germline Mutation

Figure 2A

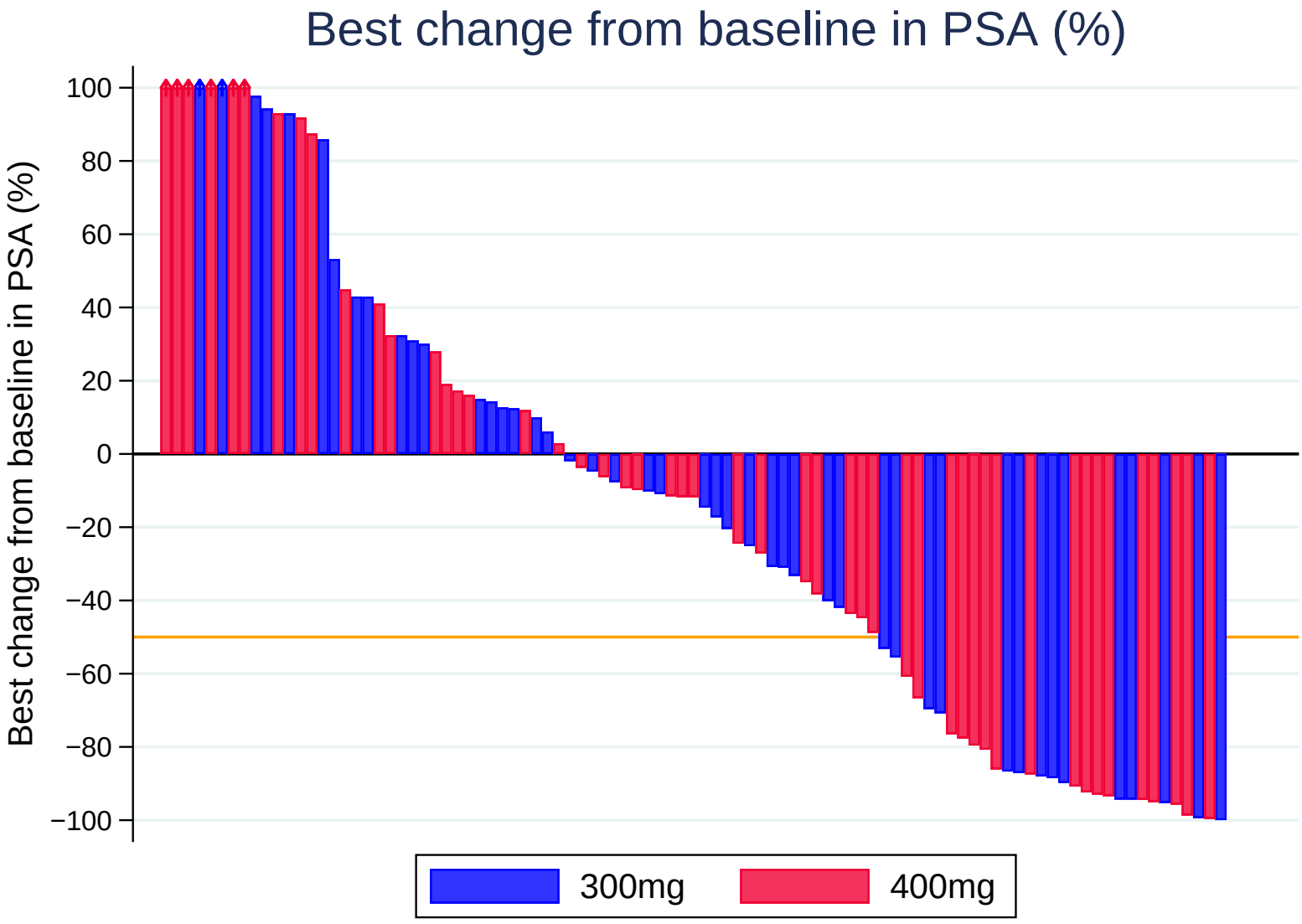

Best change from baseline in PSA (%)
Best change from baseline in PSA (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
300mg
400mg

Figure 2B

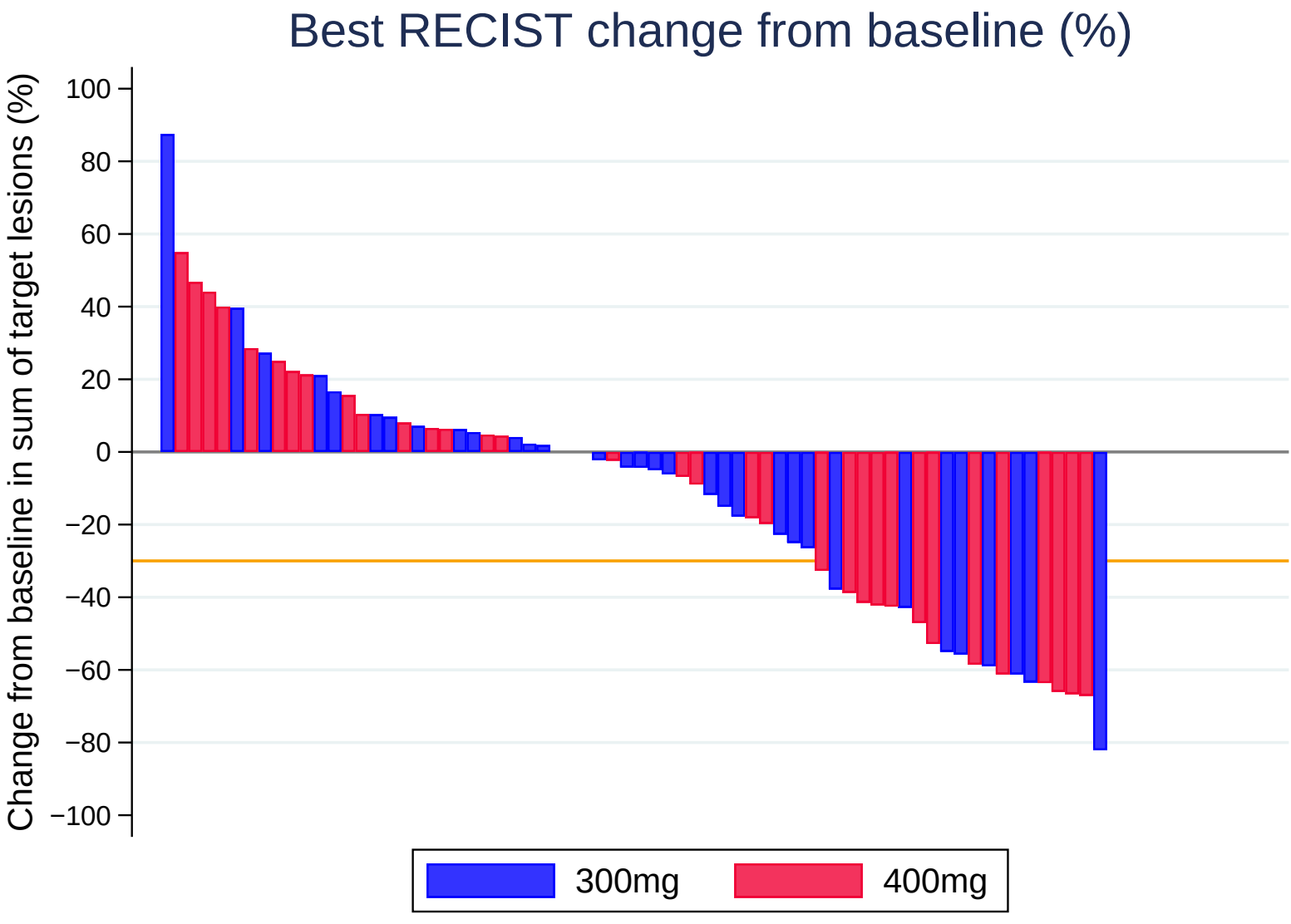
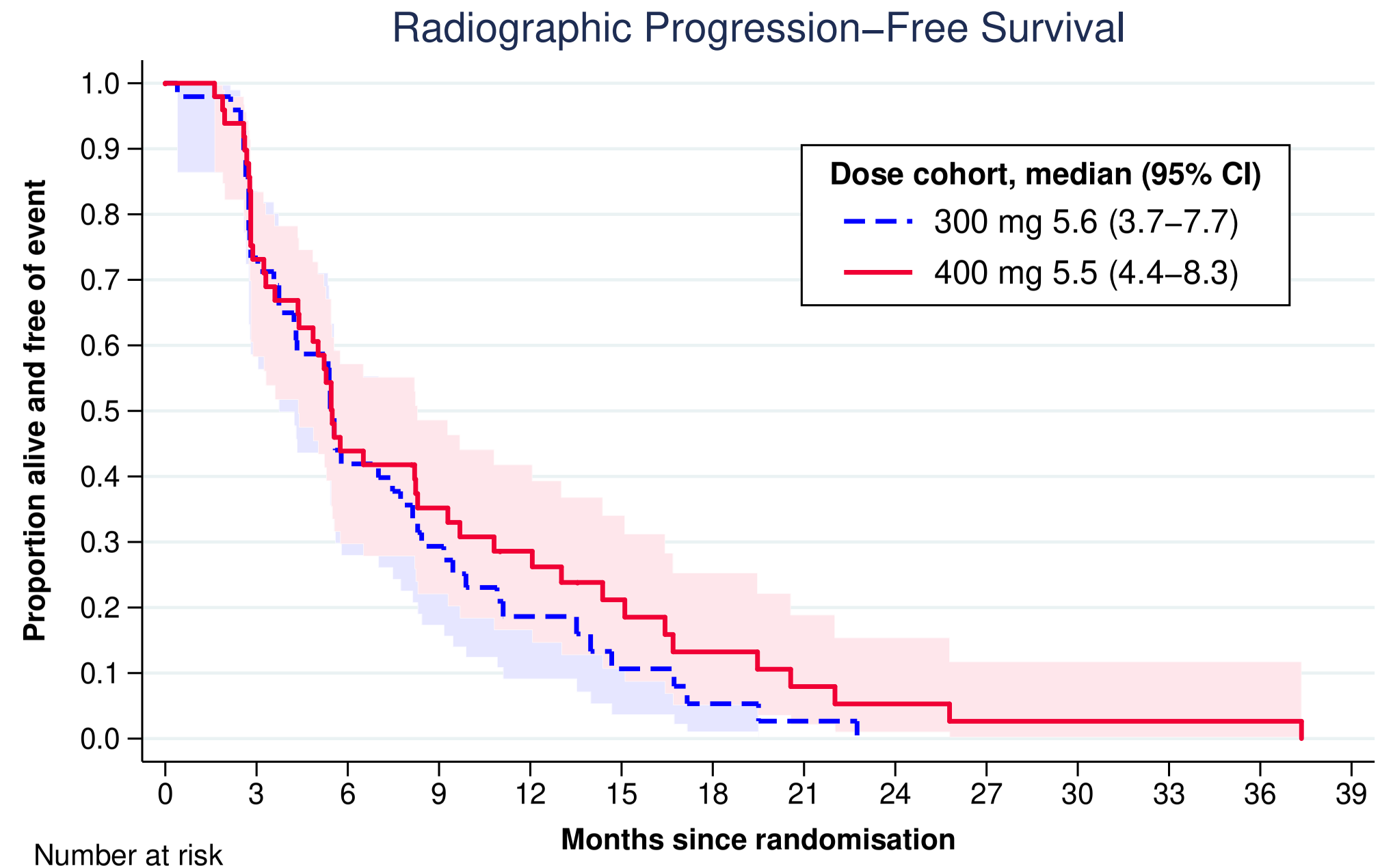

Best RECIST change from baseline (%)
Change from baseline in sum of target lesions (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
300mg
400mg

Figure 2C



Number at risk
(number censored)

300 mg	49	(1)	35	(1)	20	(1)	14	(3)	7	(3)	4	(3)	2	(3)	1	(3)	0	(3)	0	(3)	0	(3)	0	(3)
400 mg	49	(1)	35	(1)	21	(2)	16	(3)	12	(4)	8	(4)	5	(4)	3	(4)	2	(4)	1	(4)	1	(4)	1	(4)

Figure 2D

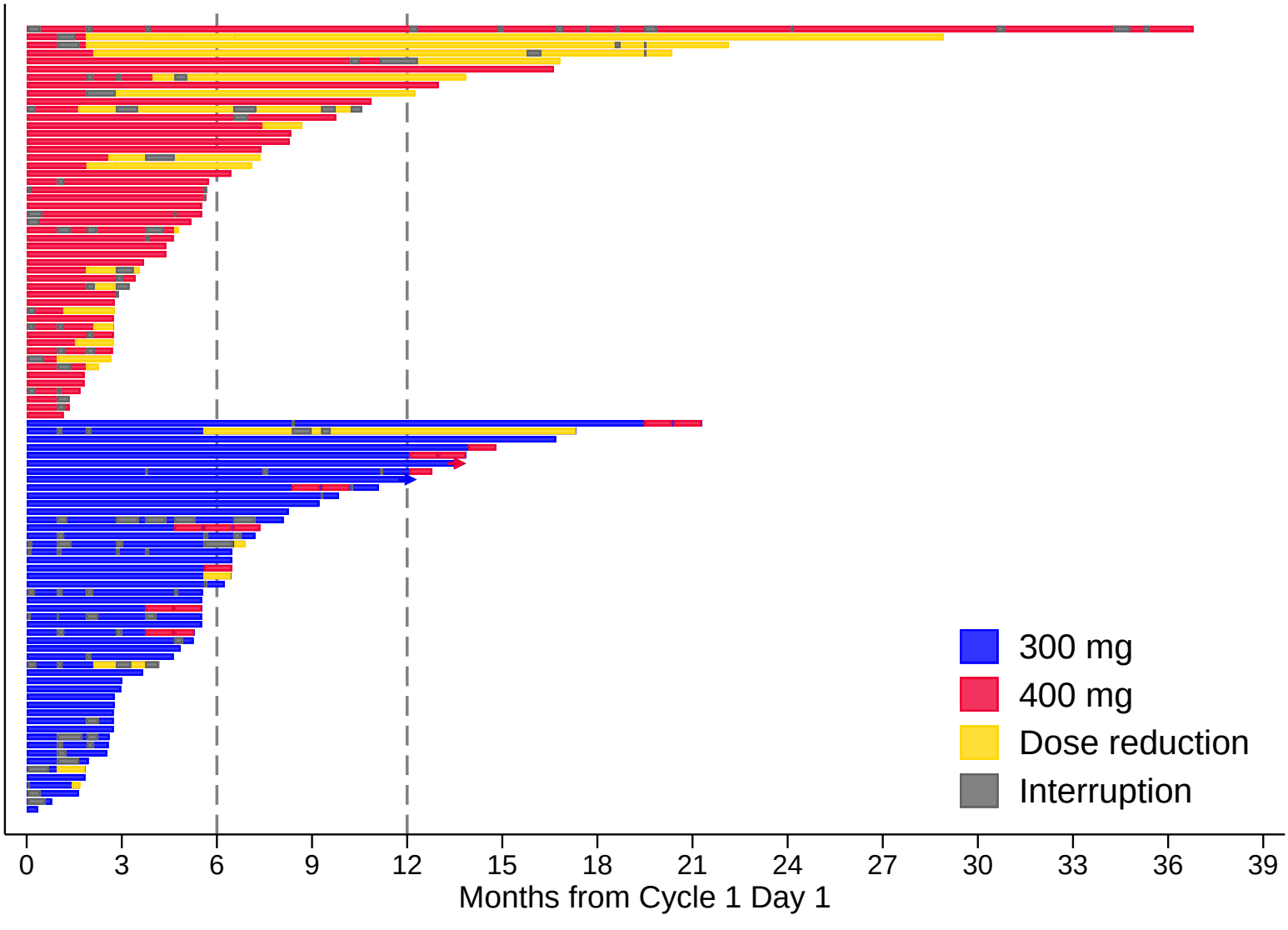

300 mg
400 mg
Dose reduction
Interruption
0
3
6
9
12
15
18
21
24
27
30
33
36
39
Months from Cycle 1 Day 1

Figure 3A

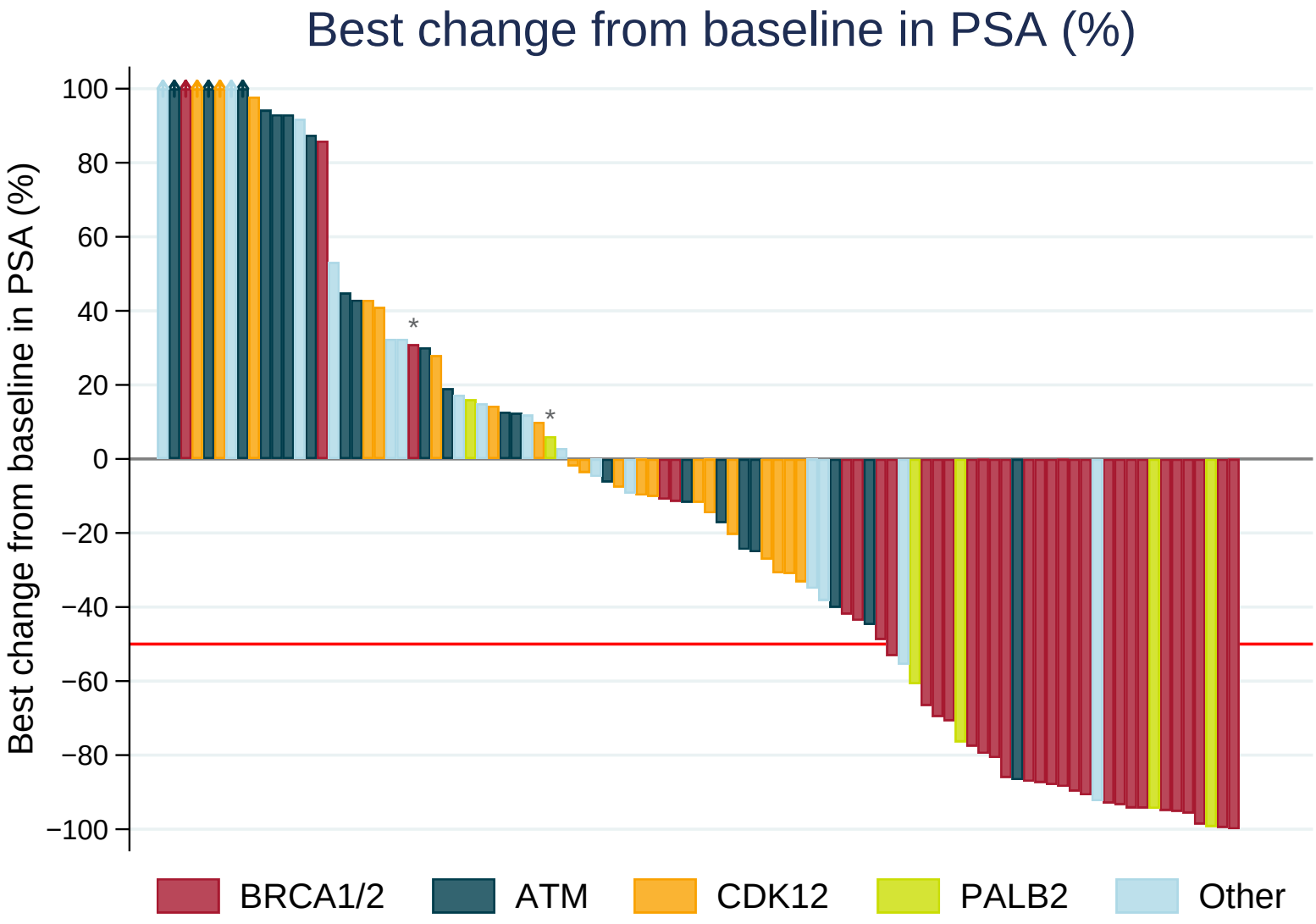
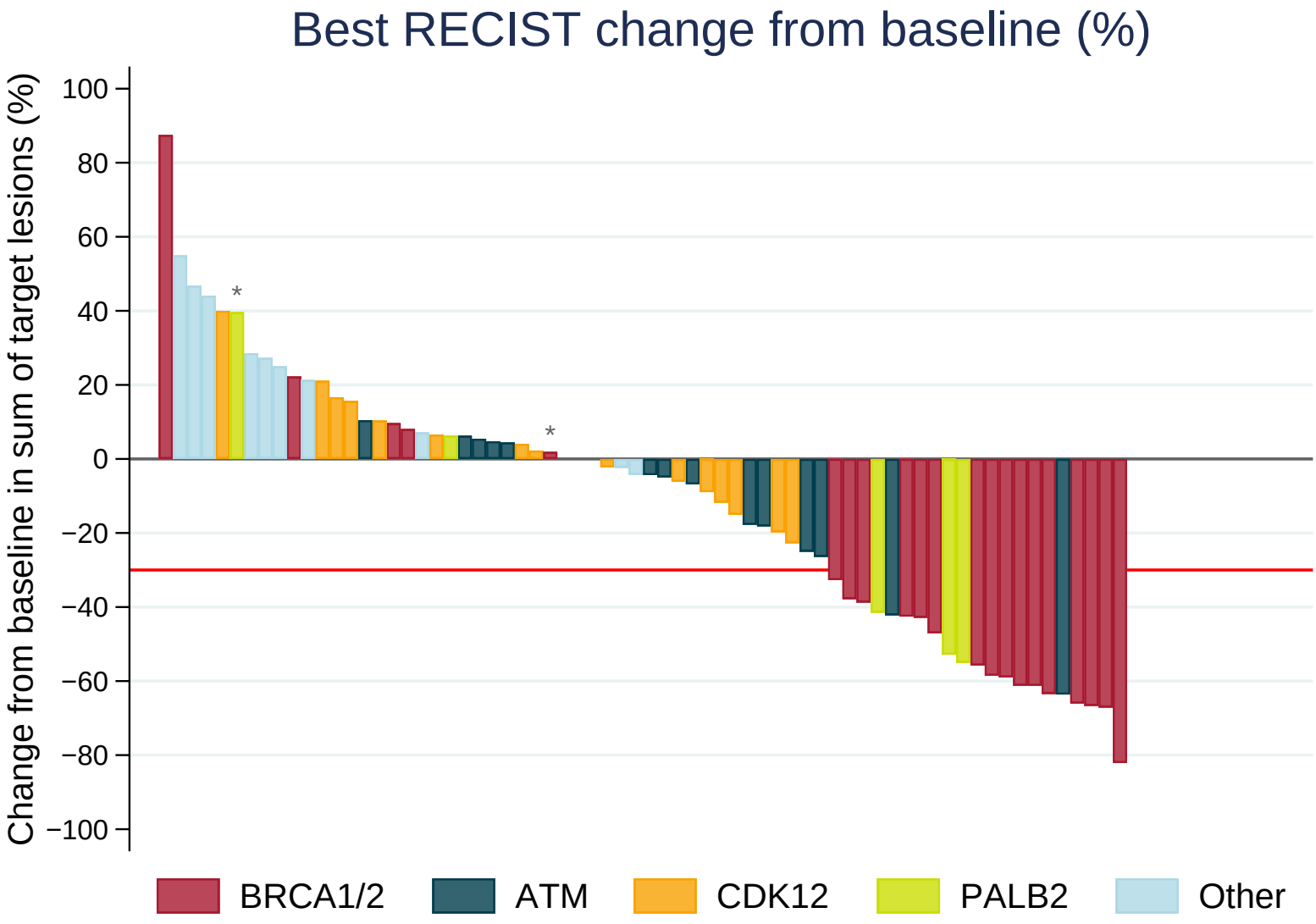
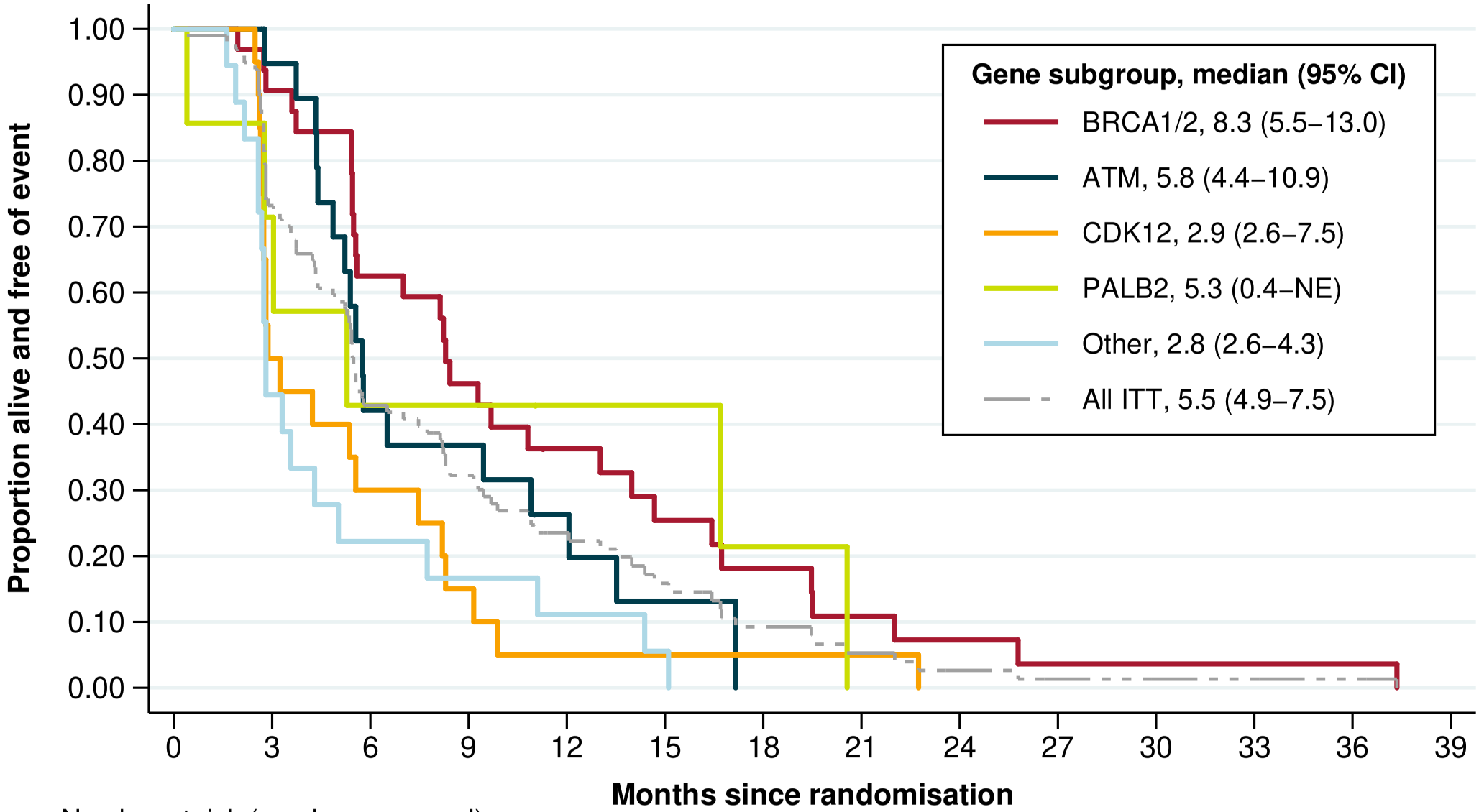

Best change from baseline in PSA (%)
Best change from baseline in PSA (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
*
*
BRCA1/2
ATM
CDK12
PALB2
Other

Figure 3B


Best RECIST change from baseline (%)
Change from baseline in sum of target lesions (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
*
*
BRCA1/2
ATM
CDK12
PALB2
Other

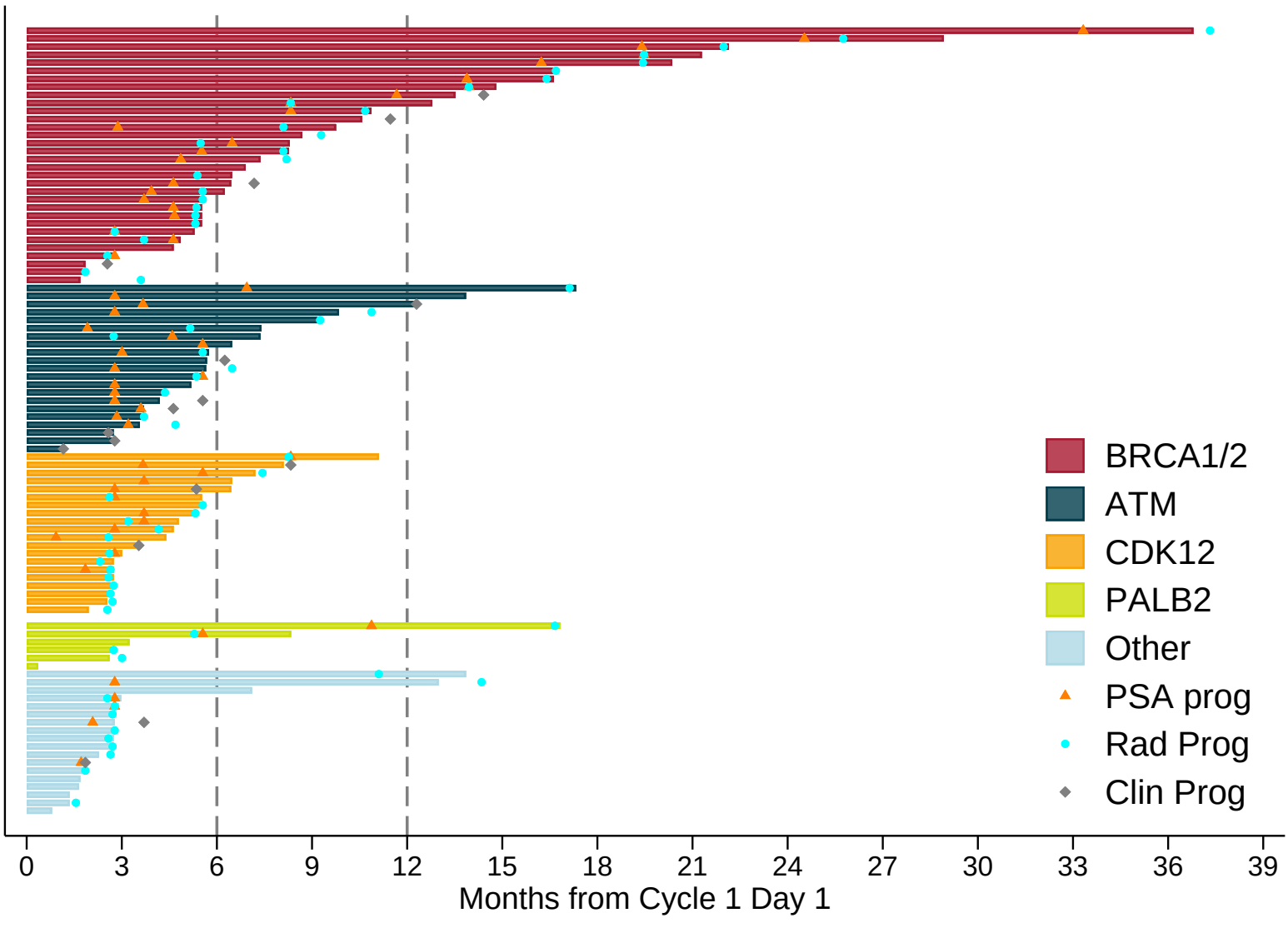
Radiographic Progression–Free Survival



Number at risk (number censored)

BRCA1/2	32	(0)	29	(0)	20	(1)	14	(2)	10	(2)	7	(2)	5	(2)	3	(2)	2	(2)	1	(2)	1	(2)	1	(2)	1	(2)
ATM	21	(2)	18	(2)	8	(2)	7	(3)	4	(4)	1	(4)	0	(4)	0	(4)	0	(4)	0	(4)	0	(4)	0	(4)	0	(4)
CDK12	20	(0)	10	(0)	6	(0)	3	(0)	1	(0)	1	(0)	1	(0)	1	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
PALB2	7	(0)	5	(0)	3	(0)	3	(1)	2	(1)	2	(1)	1	(1)	0	(1)	0	(1)	0	(1)	0	(1)	0	(1)	0	(1)
Other	18	(0)	8	(0)	4	(0)	3	(0)	2	(0)	1	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
All ITT	98	(2)	70	(2)	41	(3)	30	(6)	19	(7)	12	(7)	7	(7)	4	(7)	2	(7)	1	(7)	1	(7)	1	(7)	1	(7)

Figure 3D


BRCA1/2
ATM
CDK12
PALB2
Other
PSA prog
Rad Prog
Clin Prog
0
3
6
9
12
15
18
21
24
27
30
33
36
39
Months from Cycle 1 Day 1

TOPARP-B Supplementary Appendix

Click here to download Necessary Additional Data: TOPARP-B Supplementary Appendix Complete.pdf

CONSORT checklist

Click here to download Necessary Additional Data: TOPARP-B CONSORT 2010 Checklist.pdf