

Phase I trial of the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib and AKT inhibitor capivasertib in patients with *BRCA1/2* and non-*BRCA1/2* mutant cancers

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Conflicts of Interest

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ABSTRACT

Preclinical studies have demonstrated synergy between poly(ADP-ribose) polymerase (PARP) and phosphatidylinositol-3-kinase (PI3K)/AKT pathway inhibitors in *BRCA1* and *BRCA2* (*BRCA1/2*)-deficient and *BRCA1/2*-proficient tumors. We conducted an investigator-initiated phase I trial utilizing a prospective inpatient dose-escalation design to assess two schedules of capivasertib (AKT inhibitor) with olaparib (PARP inhibitor) in 64 patients with advanced solid tumors. Dose expansions enrolled germline *BRCA1/2*-mutant tumors, or *BRCA1/2*-wildtype cancers harboring somatic DNA damage response (DDR) or PI3K/AKT pathway alterations. The combination was well-tolerated. Recommended phase 2 doses for the two schedules were: olaparib 300mg BID with either capivasertib 400mg BID 4-days-on, 3-days-off, or capivasertib 640mg BID 2-days-on, 5-days-off. Pharmacokinetics were dose-proportional. Pharmacodynamic studies confirmed pGSK3 β suppression, increased pERK and decreased BRCA1 expression. 25 (44.6%) of 56 evaluable patients achieved clinical benefit (RECIST CR/PR or stable disease \geq 4 months), including patients with tumors harboring germline *BRCA1/2*-mutations and *BRCA1/2*-wildtype cancers with or without DDR and PI3K/AKT pathway alterations.

Running title: Phase I trial of olaparib and capivasertib in solid tumors

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STATEMENT OF SIGNIFICANCE

In the first trial to combine poly(ADP-ribose) polymerase and AKT inhibitors, a prospective inpatient dose-escalation design demonstrated safety, tolerability, pharmacokinetic-pharmacodynamic activity, and assessed predictive biomarkers of response/resistance. Antitumor activity was observed in patients harboring tumors with germline *BRCA1/2*-mutations and *BRCA1/2*-wildtype cancers with or without somatic DDR and/or PI3K/AKT pathway alterations.

INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) inhibitors are the first clinically approved drugs designed to exploit synthetic lethality in homologous recombination (HR) deficient cells, demonstrating proof of concept activity in *BRCA1/2* mutant cancers (1,2). The PARP inhibitor olaparib (Lynparza, AstraZeneca) was the first-in-class to be approved by the Food and Drug Administration (FDA) in the advanced recurrent ovarian cancer setting for women with *BRCA1/2* mutant cancers (3). Olaparib has subsequently received FDA approval in the maintenance setting for recurrent platinum-sensitive ovarian cancers regardless of *BRCA1/2* status and most recently in the first-line maintenance setting post-platinum-based chemotherapy both in women with germline or somatic *BRCA1/2* mutated advanced ovarian cancer and in patients with germline *BRCA1/2* mutated pancreatic cancer (4,5). Olaparib is also FDA approved for the treatment of patients with germline *BRCA1/2* mutant, HER2-negative metastatic breast cancers (6,7). In addition, there are now early clinical trial data in patients with tumors harboring other DNA repair aberrations (8).

Despite these broader indications, the greatest clinical benefit from PARP inhibitor monotherapy has been observed in the high grade serous germline *BRCA1/2* mutant ovarian cancer population (3). However, these patients almost inevitably develop PARP inhibitor resistance and disease progression. The utility of PARP inhibitor monotherapy in patients with different cancers harboring other DNA repair aberrations is also limited by the emergence of drug resistance and generally shortlived antitumor responses (9). Even for patients with advanced solid tumors bearing deleterious *BRCA1/2* mutations, response rates are between 30-60% depending on tumor type (3). There is therefore a major unmet need for novel

antitumor strategies to increase both the proportion of patients with clinical benefit, as well as the depth and duration of response for patients treated with PARP inhibitors (10). Such approaches include the development of rational combination strategies. Multiple preclinical studies have demonstrated synergistic antitumor activity with the combination of PARP and phosphatidylinositol-3-kinase (PI3K)/AKT pathway inhibitors in both BRCA-deficient and proficient cancer models (11-14). PI3K pathway inhibition has been shown to lead to suppression of *BRCA* gene transcription, which was accompanied by extracellular signal-regulated kinase (ERK) phosphorylation. Overexpression of an active form of MEK1 was found to result in ERK activation and downregulation of BRCA1, resulting in HR deficiency and subsequent PARP inhibitor sensitivity, thus providing strong rationale for the development of this combination as an antitumor strategy (11). A phase Ib trial of olaparib in combination with the α -specific PI3K inhibitor alpelisib demonstrated RECIST partial responses in 10 (36%) of 28 patients with ovarian cancer, providing early clinical proof-of-concept (15).

Several novel molecularly targeted agents against the PI3K-AKT pathway have now been developed, including the AKT inhibitor capivasertib (AZD5363; AstraZeneca) (16). Capivasertib is a potent and selective ATP competitive inhibitor of all 3 isoforms of AKT, which is safe and well tolerated in patients with advanced solid tumors, but with limited antitumor benefit as a single agent in early phase clinical trials (17-19). This is hypothesized to be due to multiple factors, including the development of signaling crosstalk and disruption of feedback loops, leading to acquired resistance, supporting the use of combination strategies in molecularly

defined patients for the optimal development of AKT inhibitors, such as with PARP inhibitors as described above (20,21).

Based on these promising data, we conducted an investigator-initiated phase Ib clinical trial to determine the safety, tolerability, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD) and preliminary antitumor activity of olaparib in combination with capivasertib in patients with advanced solid tumors. We also assessed a prospective inpatient dose escalation strategy where patients were permitted to prospectively increase doses of capivasertib after each cycle (if no Grade (G) 2 or worse toxicities were observed) in combination with a fixed olaparib dose. RP2D expansion cohorts were undertaken in patients with (1) germline *BRCA1/2* mutant cancers and (2) sporadic cancers with DNA damage response (DDR) aberrations or molecular abnormalities along the PI3K-AKT pathway. Detailed analyses of archived and fresh sequential tumor biopsies, as well as targeted sequencing of serial cell-free DNA (cfDNA) samples were conducted to identify determinants of response and resistance, including genomic factors and protein expression, and pharmacodynamic mechanism-of-action biomarker studies.

RESULTS

Patients

We enrolled 64 patients with advanced solid tumors from four major cancer centres in the United Kingdom into the dose escalation (20 patients) or expansion (44 patients) cohorts of this phase I trial. Characteristics of these patients are provided in **Table 1**. The most common tumor enrolled was advanced ovarian

cancer (39% of patients); these patients received a median of 5 prior therapies (range 1-12). The next most common tumor type was advanced breast cancer (28% of patients); these patients received a median number of 3 prior therapies (range 2-10).

Prospective inpatient dose escalation

The prospective inpatient dose escalation strategy utilized during each dose schedule allowed rapid, seamless and safe dose escalation, resulting in completion of the dose escalation phases of two combination schedules over 3 dose levels in 7 months (**Supplementary Figure 1**). Overall, only 10 patients were required to assess 3 different dose levels for each schedule and to establish both RP2Ds respectively.

Safety

During the dose escalation phase of the 4-days-on, 3-days-off (4/3) schedule, doses of capivasertib were increased using the prospective inpatient dose escalation design from 320mg, 400mg to 480mg BID with a fixed dose of olaparib at 300mg BID (**Supplementary Figure 1**). Of 10 patients treated in this 4/3 schedule, only 1 DLT of G3 maculopapular rash, typical of that observed with capivasertib and other AKT inhibitors, was observed at the highest dose assessed of capivasertib 480mg BID with olaparib 300mg BID (**Table 2**). The erythematous rash fully resolved after both capivasertib and olaparib were withheld, and no recurrent rash was observed after both drugs were restarted at a reduced dose of capivasertib 400mg BID with olaparib maintained at 300mg BID. At the dose level of capivasertib 480mg BID with olaparib 300mg BID administered in a 4/3 schedule, other non-DLT G3

toxicities were observed, including anemia (n=1), vomiting (n=1) and diarrhea (n=2). Due to the DLT of G3 rash, non-DLT G3 AEs and chronic low grade adverse events, e.g. fatigue and anemia, observed outside the DLT period of 21 days at the dose of capivasertib 480mg BID with olaparib 300mg BID, the SRC established the dose level of olaparib 300mg BID with capivasertib 400mg BID as the RP2D for the 4/3 schedule.

For the 2-days-on, 5-days-off (2/5) schedule of capivasertib with olaparib 300mg BID, dose escalation proceeded through dose levels of 480mg, 560mg and 640mg BID with olaparib 300mg BID. In the 10 patients treated on the 2/5 schedule, no DLTs were observed for the 2/5 schedule, and the highest dose level of capivasertib at 640mg BID with olaparib 300mg BID was selected as the RP2D. In view of similarities in overall safety, tolerability and DLT rates, the SRC elected to explore both the 4/3 and 2/5 schedules of capivasertib in the dose expansion phase.

The most common all grade treatment-emergent adverse events (TEAE) observed for all patients across both dose schedules were gastrointestinal toxicities, including nausea (67%, [grade 3-4, 4%]), diarrhea (55%, [grade 3-4, 6%]) and vomiting (41%, [grade 3-4, 5%]), as well as fatigue (51%, [grade 3-4, 5%]) (**Table 2; Supplementary Tables 1 and 2**). Other significant grade 3-4 toxicities included grade 3 anemia (10%) on the 4/3 schedule. Overall, the 4/3 schedule appeared to be less well tolerated than the 2/5 schedule, as exhibited during dose escalation: six grade 3 TEAEs (anemia and diarrhea [n=2 each]; rash and vomiting [n=1 each]) were observed with the 4/3 schedule, and only three grade 3 TEAEs (liver

transaminitis, fatigue and hyperglycemia [all n=1]) in the 2/5 schedule. No drug-related grade 4-5 toxicities were observed in either schedule.

Pharmacokinetics

Dose escalation of capivasertib showed dose dependent increases in PK exposures (**Figures 1A and 1B; Supplementary Tables 3 and 4**). The PK profile and overall concentration-time profile of capivasertib and olaparib were similar to that previously observed in single agent studies, with no significant interactions identified.

Pharmacodynamics

PD studies in platelet-rich plasma (PRP) showed significant decrease in Ser9 GSK3 β phosphorylation post-treatment at all doses in the escalation and expansion (**Figures 2A and 2B**), confirming target modulation by capivasertib. Phosphorylated ERK expression levels assessed with IHC increased in fresh tumor biopsies collected on cycle 1 day 15 compared with baseline samples in six of 8 patients, while remaining unchanged in 1 patient and decreasing in another patient (**Figure 2C**). At the same time point, BRCA1 expression decreased in paired fresh tumor biopsies obtained from all 8 patients (**Figure 2D**).

Antitumor activity

The antitumor activity of the combination of capivasertib and olaparib is detailed in **Table 3, Figures 3A-3C, and Supplementary Table 5**. Of the 56 patients who were evaluable for antitumor response, nineteen (34%) patients had RECIST PRs and/or tumor marker response (GCIG (Gynaecologic Cancer InterGroup) CA-125 response or Prostate Cancer Clinical Trials Working Group 2

(PCWG2) PSA response). Fourteen (25%) patients achieved RECIST PRs (12 confirmed and 2 unconfirmed). In addition, eleven (20%) patients had RECIST stable disease for at least 4 months (SD \geq 4 months), giving a clinical benefit rate (CBR) of 44.6% (95% CI: 31.3, 58.5). Of these 56 evaluable patients, sixteen (29%) patients were treated on study for more than 6 months, while seven (13%) patients were treated on trial for more than 1 year.

Molecular characteristics of patients with clinical benefit

Among the 25 (44.6%) patients who achieved clinical benefit (RECIST CR/PR or SD \geq 4 months), 14 (56%) patients had germline *BRCA1* or *BRCA2* mutations (ovarian cancer (n=7), breast cancer (n=5) and castration-resistant prostate cancer (CRPC; n=2)) (**Table 3; Figures 3A-3C; Supplementary Table 5**). Seven of the remaining patients had pathogenic DDR or PI3K pathway aberrations detected, while three patients did not, and one patient did not have available tissue for NGS testing.

Antitumor responses in patients with DDR and/or PI3K pathway mutations

Three RECIST-evaluable patients harboring tumors with both DDR-related and PI3K pathway mutations achieved RECIST PRs (**Figure 3B**). The mutations for these 3 patients were: (1) germline *ERCC2* mutation, somatic *PIK3CA* and *PTEN* mutations and *PTEN* IHC loss; (2) somatic *BRCA2* mutation and *PTEN* IHC loss; and (3) germline *BRCA2* and *PIK3CA* mutations, respectively. Eight of 22 (36.4%) patients with tumors harboring only DDR-related mutations achieved RECIST PR, including those with *BRCA1* (n=5), *BRCA2* (n=2) and *PALB2* (n=1) mutations. A further eight patients had a best response of SD \geq 4 months. Among those patients with tumors harboring only PI3K pathway mutations (n = 5), there was one objective

response in a patient with a tumor found to have a *PTEN* mutation. In patients with tumors harboring neither PI3K pathway nor DDR-related mutations (n=25), there were two RECIST PRs.

Patients with BRCA1/2 mutant cancers

Among 25 patients with *BRCA1/2* mutant cancers (20 with germline *BRCA1/2* mutations, 5 with somatic *BRCA1/2* mutations; breast (n=7), ovarian (n=15) and CRPC (n=3)), 22 patients had RECIST-measurable disease; 16 (72%) of these 22 patients achieved clinical benefit with the combination of olaparib and capivasertib.

Patients with advanced breast cancer

A total of 18 patients with advanced breast cancer were enrolled onto the study, 8 (44%) of whom achieved clinical benefit (**Supplementary Table 5**). Five (71.4%) out of 7 patients with *BRCA1/2* mutant breast cancer had clinical benefit; four had RECIST PR and one had SD of 19.4 weeks, with a median duration of response of 39.1 weeks (range: 14.9 – 80.9). Two of these responders with clinical benefit were platinum-resistant. None of the responding patients with advanced breast cancer had prior therapy with PARP or PI3K pathway inhibitors.

Patients with advanced ovarian cancer

There were a total of 25 patients with advanced ovarian cancer, 11 of whom achieved clinical benefit (**Supplementary Table 5**). Seven (63.6%) of these 11 patients with germline *BRCA1/2* mutant ovarian cancer achieved clinical benefit for a median duration of response of 24 weeks (range 11.3 – 115.0); 6 of these 7 patients were platinum-resistant. Four other patients with advanced ovarian cancer who also

achieved clinical benefit included those with tumors harboring (1) somatic *BRCA1*, *TP53* and *AR* mutations, (2) somatic *BRCA2* and *TP53* mutations, (3) somatic *PTEN*, *KRAS* and *SMARCA4* mutations, and (4) somatic *TP53* mutation.

Patients with advanced CRPC

Of four patients with advanced CRPC, three had germline *BRCA1/2* mutations, of whom two achieved clinical benefit (**Supplementary Table 5**). None of the 4 patients had received prior platinum-based chemotherapy.

Prior PARP inhibitor or PI3K pathway inhibitor exposed patients

Thirteen patients had prior exposure to PARP inhibitors, five of whom had clinical benefit on this combination study (**Supplementary Table 6**). One of the patients had high grade serous ovarian cancer (HGSOC) with a somatic *BRCA2* mutation, who achieved RECIST PR and GCIG CA-125 response lasting 31 weeks, while another patient with platinum-resistant germline *BRCA2* mutant HGSOC with somatic *TP53* mutation and somatic *BRCA1* VUS achieved a GCIG CA-125 response and RECIST SD lasting 56 weeks. Another patient who had previously received a PARP inhibitor had platinum-resistant HGSOC harboring a germline *BRCA2* mutation and achieved a GCIG CA-125 response and RECIST SD on this trial lasting 115 weeks. Only one patient had previously received a PI3K pathway inhibitor prior to this clinical trial; she was a patient with advanced peritoneal mesothelioma who had previously achieved a RECIST PR on a single agent PI3K pathway inhibitor prior to eventually progressing. On this clinical trial, she achieved a CA-125 response by GCIG criteria and durable RECIST SD lasting 84 weeks before progression.

Cell-free DNA analysis

A total of 157 cfDNA samples were serially collected from 41 patients for analysis on a targeted NGS panel. Of these patients, at least one mutation was detected in baseline cfDNA samples from 38 (93%) patients. Of 39 patients where both tumor and cfDNA samples were available for analysis, mutation status at baseline was concordant between tumor and cfDNA samples in 34 (87.2%) patients. All germline and somatic mutations detected through germline and/or tumor testing were detected in cfDNA. The most common mutations detected in cfDNA included *TP53* (n=26 [63.4%] patients), *BRCA2* (n=11 [26.8%]), *BRCA1* (n=7 [17.1%]), *KRAS* (n=4 [9.8%]), *PIK3CA* (n=3 [7.3%]), *ARID1A* (n=3 [7.3%]) and *PTEN* (n=2 [4.9%]).

The cfDNA allele frequencies of somatic mutations decreased in selected responding patients and increased upon disease progression (**Supplementary Figures 2A-2F**). In patients with known germline mutations, e.g. *BRCA1/2* mutations, falls in the cfDNA allele frequencies of germline mutations toward 50% were observed as they responded to trial therapy (**Supplementary Figures 2C-2D**). Of 20 patients harboring germline and/or somatic *BRCA1/2* mutations with available cfDNA sampling, 5 patients were found to have *BRCA1/2* reversion mutations at disease progression in their end of treatment cfDNA samples (**Supplementary Table 7**). One of these patients with advanced ovarian cancer, who had early disease progression after 4 weeks on trial, had a tumor somatic *BRCA1* mutation (c.329insA, p.K110fs*4) in archived tissue, but was found to have a secondary *BRCA1* mutation deletion restoring the original reading frame (c.335_338delATAA)

in her cfDNA sample collected at baseline on cycle 1 day 1 and at disease progression.

DISCUSSION

In this study, we have shown that the novel combination of olaparib and capivasertib is well tolerated at biologically effective doses that achieve clinical benefit, including durable responses, in patients with a range of treatment-refractory cancers, including both germline *BRCA1/2* mutated tumors, and sporadic cancers harboring actionable somatic alterations. Antitumor responses were also observed in patients who had previously developed disease progression on PARP and PI3K pathway inhibitors.

Two different intermittent schedules of capivasertib were assessed to determine differences in safety, tolerability, PK-PD activity and antitumor responses in combination with olaparib, by comparing a high dose of capivasertib given over a shorter 2/5 schedule versus a lower dose of capivasertib over a longer 4/3 schedule. Overall, this combination was generally well tolerated in both schedules; treatment-related toxicities were reversible and mainly GI-related, including diarrhea, mucositis, nausea and anorexia. Such potential overlapping GI toxicities were effectively managed with simple supportive measures when indicated clinically, such as antiemetics and anti-diarrheals. No DLTs were observed on the 2/5 schedule, while 1 DLT of reversible grade 3 rash was observed at the highest tested dose of 480mg BID of capivasertib with 300mg BID of olaparib in the 4/3 schedule. Dose proportional PKs were observed, and proof-of-mechanism PD studies confirmed AKT pathway modulation across dose levels in platelet-rich plasma. Two different

combination RP2Ds were established – 400mg BID of capivasertib with 300mg BID of olaparib for the 4/3 schedule, and 640mg BID of capivasertib with 300mg BID of olaparib with for the 2/5 schedule.

This study employed a prospective inpatient dose escalation trial design, which enabled the rapid completion of dose escalation phases of two different combination schedules, each involving 3 dose levels, within 7 months and only requiring a total of 10 patients in each schedule. Apart from optimizing speed and minimizing patient numbers, this prospective inpatient dose escalation has benefits over established Phase I escalation strategies including minimization of patient numbers receiving subtherapeutic drug doses, and safe optimization of drug exposures at an individual level to ensure maximal blockade of critical targets for combination strategies.

In preclinical studies, inhibition of the PI3K pathway has been shown to lead to upregulation of poly-ADP-ribosylation (PAR) and phosphorylation of H2AX, indicating increased DNA damage in cells (12). The accumulation of unrepaired DNA double stranded breaks in BRCA-deficient cells in turn make them exquisitely sensitive to PARP inhibition, potentially accounting for the synergistic effects seen in combined olaparib and capivasertib treatment. Apart from germline BRCA mutant breast cancers, preclinical studies have also demonstrated that PI3K inhibition in triple negative breast cancer (TNBC) models drives ERK-dependent activation of the ETS transcription factor, which suppresses *BRCA* gene transcription, causing a deficiency of HR activity and PARP inhibitor sensitivity (11). Correlative tumor studies from this study have shown increases in tumor phosphorylated ERK

expression associated with decreases in BRCA1 expression levels, supporting this hypothesis and rationale for this novel combination (14). Given that ERK phosphorylation may potentially have negative protumor consequences as well, future studies should investigate if this may represent a compensatory response that blunts antitumor efficacy.

The combination of olaparib and capivasertib on both 4/3 and 2/5 schedules have shown evidence of antitumor activity, with clinical benefit observed in 44.6% of evaluable patients on study. Fourteen (56%) of these 25 responding patients harbored germline *BRCA1/2* mutations, while 8 (32%) of 25 had relevant somatic aberrations, including *BRCA2*, *PIK3CA*, *PTEN*, and *PALB2* mutations (**Figure 3A**). All three patients with tumors harboring both DDR-related and PI3K pathway related aberrations had RECIST PRs, eight of 23 evaluable patients with tumors harboring only DDR-related tumor mutations achieved RECIST PR, and 1 of 5 patients deficient for *PTEN* had a RECIST PR (**Figures 2B-2C**). Importantly, clinical benefit was also observed in patients with neither PI3K pathway nor DDR-related tumor mutations detected, as well as in patients who had previously progressed on PARP or PI3K pathway inhibitors. While based on small numbers, these findings are in keeping with preclinical studies, which indicate that efficacy is not necessarily confined to tumors with actionable mutations such as *BRCA1/2* mutations (11,12). Regardless, a suitably-powered randomized trial will be necessary to formally determine if there is synergistic patient benefit in the clinic with this capivasertib and olaparib combination.

In this study, concordance in the detection of selected mutations between cfDNA and tumor was 87.2%, supporting the use of cfDNA for the contemporaneous molecular profiling of patients. This high concordance may be associated with the large proportion of patients with germline mutation cancers included in this trial. Similar to previous studies (22), the cfDNA allele frequencies of somatic mutations decreased in selected responding patients and increased upon disease progression. Falls in the allele frequencies of germline mutations toward 50% were observed as they responded to trial therapy, suggesting elimination of the tumor clone (22). The development of *BRCA1/2* reversion mutations was observed at disease progression in cfDNA from five (25%) out of 20 patients with *BRCA1/2* mutant cancers with available cfDNA for analysis (**Supplementary Table 7**). This finding supports BRCA reversion as a likely resistance mechanism in PARP inhibitor-based therapies, including regimens such as this olaparib-capivasertib combination, and advocates the use of serial cfDNA sampling longitudinally in detecting the emergence of such aberrations. The patient with a *BRCA1* reversion mutation detected in cfDNA at baseline and again at early disease progression had primary resistance to this combination, suggesting that the detection of such aberrations in cfDNA should also be considered as part of screening tests prior to PARP inhibitor based therapies (22,23).

Five (71.4%) out of 7 patients with germline *BRCA1/2* mutant breast cancers achieved clinical benefit. In the phase 3 OlympiAD trial where patients with germline *BRCA1/2* mutant HER2-negative metastatic breast cancer were randomized to receive olaparib or single-agent chemotherapy of the physician's choice, the response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy

group (6). Although based on small numbers, our study provides preliminary clinical data that supports the combination of capivasertib with olaparib as a rational strategy to potentially improve patient benefit beyond that of single agent olaparib. The addition of capivasertib to first line paclitaxel chemotherapy for TNBC was also shown to lead to significantly longer progression-free survival (PFS) and overall survival (OS) in a randomized, double-blind, placebo-controlled phase 2 trial, particularly in patients with tumors harboring *PIK3CA/AKT1/PTEN* alterations (24). In addition, the FAKTION phase 2 trial showed that the addition of capivasertib to fulvestrant in patients with endocrine-resistant, advanced estrogen receptor positive breast cancer also resulted in significantly longer PFS and an observed OS improvement of approximately 6 months, although this was not statistically significant (37% OS data maturity) (25). Phase 3 trials of capivasertib-based combinations are planned or ongoing.

We observed clinical benefit in 7 of 10 patients (median duration of response for these responders was 24 weeks, range 11.3 – 115.0) with germline *BRCA1/2* mutant ovarian cancer, of which 6 were platinum-resistant. Overall, 6 (24%) of 25 patients with advanced ovarian cancer achieved RECIST PR, while 5 (20%) had RECIST SD. An ongoing Phase Ib/2 trial of olaparib and capivasertib in patients with advanced ovarian, endometrial and triple negative breast cancer used the combination RP2D established in this trial of 400mg BID of capivasertib with 300mg BID of olaparib in the 4/3 schedule. Preliminary results from this trial have shown a RECIST PR rate of 7 (24%) of 30 patients, including RECIST PRs in four of 8 patients with recurrent endometrial cancer, 2 patients with TNBC and 1 patient with ovarian cancer, as well as RECIST SD \geq 4 months in 6 additional patients (26). This

compares with 10 (36%) of 28 patients with ovarian cancer achieving RECIST PR, and 14 (50%) attaining RECIST SD in the phase Ib trial of olaparib in combination with the α -specific PI3K inhibitor alpelisib (15).

In summary, capivasertib in combination with olaparib was well tolerated in both 4/3 and 2/5 schedules. Blockade of AKT led to a downregulation of pSer9 pGSK3 β , indicating target modulation, while increased pERK and decreased BRCA1 expression provided translational mechanistic insights into potential synergistic activity between capivasertib and olaparib. Antitumor activity was observed more frequently in patients with either germline *BRCA1/2* mutant cancers and sporadic cancers with somatic aberrations along the DDR and PI3K/AKT pathways. There were also preliminary signals of clinical benefit in platinum-resistant HGSOC and in patients who had received prior PARP inhibitors. Our results support the development of the combination of olaparib and capivasertib as a promising strategy that warrants further exploration in future clinical trials.

METHODS

This investigator-initiated study (ClinicalTrials.gov: NCT02338622) was designed by TAY and JDB, with support from AstraZeneca, and conducted in accordance with the provision of the Declaration of Helsinki and Good Clinical Practice guidelines. Dose escalation was conducted at the Royal Marsden NHS Foundation Trust (RM), London, UK, while the dose expansion phase also involved University College London Hospital, London, Northern Centre for Cancer Care, Newcastle, and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. The Central London Research Ethics Committee (REC) approved the protocol

(REC reference 14/LO/0103). The trial was co-sponsored by the Institute of Cancer Research (ICR) and RM, and centrally managed by the Drug Development Unit (Investigator Initiated Trials Team) at the ICR/RM. Funding was provided by the Experimental Cancer Medicine Centres (ECMC) network, National Institute of Health Research, Cancer Research UK (CR-UK), and AstraZeneca.

Study population

Eligible patients had histologically confirmed advanced solid tumors refractory to standard therapies and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1. Complete eligibility criteria are available in the Data Supplement. Dose expansion cohorts mandated patients with germline *BRCA1/2* mutated tumors (Cohort A) or germline *BRCA1/2* wildtype patients with sporadic tumors likely to harbor HR defects or demonstrating somatic aberrations known to result in a hyperactivated PI3K-AKT pathway (or defective DNA repair) (Cohort B). The dose escalation cohort was enriched for patients with characteristics mandated in expansion cohorts A and B, but this was not a requirement. Written informed consent was obtained from all patients.

Trial design

This was an open-label, multicenter phase Ib trial assessing the combination of olaparib and capivasertib in patients with advanced solid tumors. The primary objectives were to determine the safety and tolerability of olaparib in combination with capivasertib, and to establish a MTD and/or RP2D of this combination. Secondary objectives included the characterization of PK and PD profiles of both agents in combination. Exploratory objectives included the assessment of

preliminary antitumor activity of the combination and evaluation of putative predictive biomarkers of response and resistance. Study conduct was overseen by a Safety Review Committee (SRC), comprising the Chief Investigator, Principal Investigator or delegate from each investigational site, DDU Pharmacovigilance Officer or delegate, CR-UK's Drug Development Office medical advisor or delegate, an observer from AstraZeneca, a Clinical Trials Manager or delegate, an independent senior ECOM network clinician and a RMH representative who was independent of the study team.

Prospective inpatient dose escalation

This phase I trial utilized a prospective inpatient dose escalation trial design, where doses of cypivasertib were prospectively escalated in each patient in combination with a fixed continuous dose of olaparib (**Supplementary Figure 1; Supplementary Methods**).

Toxicities and laboratory variables were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients had safety evaluations weekly and tumor response assessments after every three treatment cycles, using computer tomography scans evaluated by RECIST version 1.1. As appropriate, different tumor markers were used to assess the effects of study treatment on respective tumor types, e.g. serum CA-125 was assessed in patients with ovarian cancer according to GCI criteria or serum PSA levels in patients with CRPC according to PCWG2 criteria.

Pharmacokinetics and pharmacodynamics

PK modelling was conducted using a non-compartmental extravascular model for plasma with Phoenix™ WinNonLin Software® version 64 (Pharsight). PD Biomarker analysis of pSer9 GSK3β was undertaken on PRP where available, using assays validated to Good Clinical Practice standards on the MesoScale Discovery (MSD®) technology platform (**Supplementary Methods**) (27). ERK expression was assessed using immunohistochemistry conducted on formalin-fixed, paraffin-embedded (FFPE) tissue sections (**Supplementary Methods**). BRCA1 expression was assessed using a BRCA1 pan-nuclear IHC staining (**Supplementary Methods**).

Predictive biomarker studies

Targeted next generation sequencing studies were conducted on patients with available tumor tissue at the Institute of Cancer Research (**Supplementary Methods**); libraries were constructed with the use of GeneRead DNA seq Panel (Qiagen) and run on a MiSeq sequencer (Illumina). Whole exome sequencing was also performed on germline and tumor DNA of responding patients using Illumina HiSeq 2500 in paired-end mode. Variants are annotated as pathogenic if considered 'pathogenic' or 'likely pathogenic' according to the ClinVar database (28) and/or ACMG classification using VarSome (29). PTEN loss was assessed by immunohistochemistry performed on FFPE tissue sections from archived tumor where available as previously described (30).

Statistical analysis

Analysis was conducted after all patients had received 1 cycle of treatment and had completed their last study visit conducted 28 days after the last dose of

combination treatment. Patients were evaluable for antitumor efficacy assessment if they had at a baseline RECIST assessment and at least one post-baseline RECIST assessment. Under the assumption that the true underlying CBR was 20%, with anticipated recruitment of 40 patients in the expansion phase, there would be a <1% chance of seeing no responses, and a >99% chance of observing 2 or more responses.

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Table 1: Patient Demographics

Characteristic	Olaparib 300mg BID and Capivasertib BID either 4-days-on, 3-days-off or 2-days-on, 5-days-off schedule		Total n=64 (100%)
	4-days-on, 3-days-off Schedule, n=33 (52%)	2-days-on, 5-days-off Schedule, n=31 (48%)	
Median age, years (range)	59 (32-76)	54 (32-72)	57 (32-76)
Gender No. (%)			
Male	6 (18)	5 (16)	11 (17)
Female	27 (82)	26 (84)	53 (83)
ECOG PS, No. (%)			
ECOG PS 0	13 (39)	9 (29)	22 (34)
ECOG PS 1	20 (61)	22 (71)	42 (66)
Tumor, No. (%)			
Ovarian	13 (39) [7 germline <i>BRCA1/2</i> ; 4 somatic <i>BRCA1/2</i>]	12 (39) [4 germline <i>BRCA1/2</i> ; 1 somatic <i>BRCA1/2</i>]	25 (39)
Breast	8 (24) [2 germline <i>BRCA1/2</i>]	10 (32) [5 germline <i>BRCA1/2</i> ; 1 germline <i>PALB2</i>]	18 (28)
Pancreatic	3 (9)	2 (7)	5 (8)
CRPC	2 (6) [1 germline <i>BRCA1/2</i>]	2 (7) [2 germline <i>BRCA1/2</i>]	4 (6)
Cervical	2 (6)	-	2 (3)
Endometrial	1 (3)	1 (3)	2 (3)
Bladder	1 (3)	-	1 (1.5)
Colorectal	1 (3)	-	1 (1.5)
Cholangiocarcinoma	-	1 (3)	1 (1.5)
GIST	-	1 (3)	1 (1.5)
Cancer of unknown origin (CUP)	1 (3)	-	1 (1.5)
Pleural mesothelioma	-	1 (3)	1 (1.5)
Peritoneal mesothelioma	-	1 (3)	1 (1.5)
Carcinosarcoma (uterine)	-	1 (3)	1 (1.5)
Median prior lines of systemic therapy, No. (range)			
Ovarian (n=25)	3 (1-10)	5 (1-12)	4 (1-12)
Breast (n=18)	3 (2-10)	4 (3-9)	3 (2-10)

Table 2: Treatment-Related Adverse Events during dose escalation

Table 2A: Treatment-Related Adverse Events (maximum grade, all cycles) for olaparib 300mg BID and capivasertib 4-days-on, 3-days-off schedule during dose escalation

		Olaparib 300mg BID and Capivasertib BID 320mg (n=6)				Olaparib 300mg BID and Capivasertib BID 400mg (n=7)				Olaparib 300mg BID and Capivasertib BID 480mg (n=6)			
		Grade 1 or 2		Grade 3 or 4		Grade 1 or 2		Grade 3 or 4		Grade 1 or 2		Grade 3 or 4	
Specific Organ Class	Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders	Anemia	0	0.0	0	0.0	1	14.3	1	14.3	2	33.3	1	16.7
	Neutropenia	1	16.7	0	0.0	1	14.3	0	0.0	1	16.7	0	0.0
	Thrombocytopenia	1	16.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Gastrointestinal disorders	Abdominal pain	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	0	0.0
	Constipation	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Diarrhea	2	33.3	0	0.0	0	0.0	0	0.0	1	16.7	2	33.3
	Melena	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	0	0.0
	Mouth ulceration	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	0	0.0
	Nausea	5	83.3	0	0.0	1	14.3	0	0.0	5	83.3	0	0.0
	Vomiting	1	16.7	0	0.0	3	42.9	0	0.0	1	16.7	1	16.7
General disorders and administration site conditions	Fatigue	4	66.7	0	0.0	2	28.6	0	0.0	4	66.7	0	0.0
	Mucosal inflammation	2	33.3	0	0.0	2	28.6	0	0.0	1	16.7	0	0.0
Musculoskeletal and connective tissue disorders	Myalgia	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
Nervous system disorders	Dizziness	1	16.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Dysgeusia	1	16.7	0	0.0	1	16.7	0	0.0	0	0.0	0	0.0
Renal and urinary disorders	Hematuria	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	0	0.0
Skin and subcutaneous tissue disorders	Dry skin	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Eczema	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Pruritus	1	16.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Rash	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Rash maculo-papular	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7

Table 2B: Treatment-Related Adverse Events (maximum grade, all cycles) for olaparib 300mg BID and capivasertib BID 2-days-on, 5-days-off schedule during dose escalation

		Olaparib 300mg BID and Capivasertib BID 480mg (n=8)				Olaparib 300mg BID and Capivasertib BID 560mg (n=6)				Olaparib 300mg BID and Capivasertib BID 640mg (n=6)			
		Grade 1 or 2		Grade 3 or 4		Grade 1 or 2		Grade 3 or 4		Grade 1 or 2		Grade 3 or 4	
Specific Organ Class	Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders	Anemia	0	0.0	0	0.0	2	33.3	0	0.0	3	50.0	0	0.0
	Neutropenia	0	0.0	0	0.0	1	16.7	0	0.0	0	0.0	0	0.0
Gastrointestinal disorders	Abdominal distension	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Abdominal pain	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Diarrhea	5	62.5	0	0.0	1	16.7	0	0.0	3	50.0	0	0.0
	Gastro-esophageal reflux disease	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Nausea	6	75.0	0	0.0	1	16.7	0	0.0	1	16.7	0	0.0
	Vomiting	1	12.5	0	0.0	2	33.3	0	0.0	2	33.3	0	0.0
General disorders and administration site conditions	Fatigue	4	50.0	0	0.0	2	33.3	1	16.7	3	50.0	0	0.0
	Mucosal inflammation	0	0.0	0	0.0	1	16.7	0	0.0	1	16.7	0	0.0
Infections and infestations	Oral candidiasis	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
Investigations	Transaminases increased	0	0.0	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0
Metabolism and nutrition disorders	Decreased appetite	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Hyperglycemia	0	0.0	1	12.5	0	0.0	0	0.0	1	16.7	0	0.0
	Hypokalemia	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Nervous system disorders	Dysgeusia	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
Renal and urinary disorders	Glycosuria	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders	Cough	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Dyspnea	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
	Wheezing	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
Skin and subcutaneous tissue disorders	Nail ridging	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 3: Characteristics of patients who achieved clinical benefit (RECIST CR/PR or SD≥4 months)

Responder Patient No.	Tumor	Pathogenic germline mutation	Pathogenic somatic mutation	Platinum status if known	Prior PARP inhibitor	Prior PI3K pathway inhibitor	PTEN IHC	Best response of RECIST CR/PR	Best response of RECIST SD≥4 months	Tumor marker response	Dose Schedule	Escalation (highest dose) or Expansion	Duration on treatment (weeks)
1	Breast	BRCA2	BRCA2, PIK3CA	RESISTANT	-	-	-	cPR	Yes	cPR	2d-on, 5d-off	Escalation (640mg)	81
2	Breast	None detected	ERBB2, PIK3CA	-	-	-	-	SD	Yes	-	4d-on, 3d-off	Escalation (480mg)	36
3	Breast	BRCA1	BRCA1, TP53	-	-	-	-	cPR	Yes	-	4d-on, 3d-off	Escalation (480mg)	39
4	Breast	BRCA2, RAD51D	BRCA2, RAD51D, ARID1A	RESISTANT	-	-	-	SD	Yes	-	2d-on, 5d-off	Expansion	18
5	Breast	BRCA1	BRCA1, TP53	SENSITIVE	-	-	-	cPR	Yes	-	2d-on, 5d-off	Expansion	51
6	Breast	PALB2	PALB2	-	-	-	-	cPR	Yes	cPR	2d-on, 5d-off	Expansion	66
7	Breast	BRCA1	BRCA1, TP53	-	-	-	-	uPR	Yes	-	4d-on, 3d-off	Expansion	15
8	Breast	None detected	None detected	SENSITIVE	-	-	-	cPR	Yes	-	2d-on, 5d-off	Expansion	36
9	Endometrial cancer	ERCC2	ERCC2, PIK3CA, PTEN, TP53, TSC1	SENSITIVE	-	-	PTEN loss	cPR	Yes	cPR	4d-on, 3d-off	Expansion	29
10	Ovarian	BRCA1	BRCA1, TP53	RESISTANT	PARP inhibitor resistant	-	-	SD	Yes	-	2d-on, 5d-off	Escalation (640mg)	18
11	Ovarian	None detected	TP53	SENSITIVE	-	-	-	cPR	Yes	cPR	2d-on, 5d-off	Escalation (640mg)	27
12	Ovarian	BRCA2	BRCA2, TP53	RESISTANT	PARP inhibitor exposed	-	-	SD	Yes	-	4d-on, 3d-off	Escalation (400mg)	24
13	Ovarian	BRCA1	BRCA1, TP53	RESISTANT	-	-	-	cPR	Yes	cPR	2d-on, 5d-off	Escalation (480mg)	33

Responder Patient No.	Tumor	Pathogenic germline mutation	Pathogenic somatic mutation	Platinum status if known	Prior PARP inhibitor	Prior PI3K pathway inhibitor	PTEN IHC	Best response of RECIST CR/PR	Best response of RECIST SD≥4 months	Tumor marker response	Dose Schedule	Escalation (highest dose) or Expansion	Duration on treatment (weeks)
14	Ovarian	BRCA1	BRCA1, TP53	RESISTANT	-	-	-	uPR	Yes	-	2d-on, 5d-off	Expansion	18
15	Ovarian	None detected	BRCA2, TP53	SENSITIVE	PARP inhibitor resistant	-	PTEN loss	cPR	Yes	cPR	4d-on, 3d-off	Expansion	31
16	Ovarian	BRCA2	BRCA2 (Plasma only)	RESISTANT	PARP inhibitor resistant	-	-	SD	Yes	cPR	4d-on, 3d-off	Expansion	115
17	Ovarian	None detected	PTEN, KRAS, SMARCA4	RESISTANT	-	-	-	cPR	Yes	cPR	4d-on, 3d-off	Expansion	83
18	Ovarian	None detected	BRCA1, AR, TP53	RESISTANT	-	-	-	SD	Yes	cPR	4d-on, 3d-off	Expansion	18
19	Ovarian	BRCA2	BRCA2, TP53	RESISTANT	PARP inhibitor resistant	-	-	SD	Yes	cPR	4d-on, 3d-off	Expansion	56
20	Ovarian	BRCA2	BRCA2, NF1, TP53	SENSITIVE	-	-	-	cPR	No	uPR	4d-on, 3d-off	Expansion	11
21	Peritoneal mesothelioma	None detected	None detected	SENSITIVE	-	PI3K inhibitor resistant	-	SD	Yes	cPR	4d-on, 3d-off	Escalation (480mg)	84
22	Pleura mesothelioma	None detected	None detected	SENSITIVE	-	-	-	SD	Yes	-	2d-on, 5d-off	Escalation (640mg)	16
23	Prostate	RAD51D, NTRK1	RAD51D, NTRK1	-	-	-	-	SD	Yes	-	4d-on, 3d-off	Escalation (480mg)	18
24	Prostate	BRCA2	BRCA2, CDKN1B	-	-	-	-	SD	Yes	cPR	4d-on, 3d-off	Escalation (400mg)	98
25	Prostate	BRCA2	BRCA2, TP53	-	-	-	-	cPR	Yes	cPR	2d-on, 5d-off	Expansion	21

TABLE LEGENDS

Table 1: Patient Demographics

Table 2: Treatment-Related Adverse Events during dose escalation

Table 3: Characteristics of patients who achieved clinical benefit.

FIGURES

Figure 1: Dose proportionality of Capivasertib during intra-patient dose escalation in both the 4-days-on, 3-days-off (Figure 1A) and 2-days-on, 5-days-off (Figure 1B) schedules.

PK modelling was conducted using a non-compartmental extravascular model for plasma using PhoenixTM WinNonLin Software[®] version 64 (Pharsight). Once the PK parameters were established for each patient, the mean AUC to the last sampled time point at 12 hours were plotted against the capivasertib dose administered.

Figure 2A: Pharmacodynamic profile of capivasertib and olaparib in serially collected PRP during intra-patient dose escalation on a 4 days on 3 days off schedule.

Platelet rich plasma was collected from patients at baseline and pre-dose on day 4 (4/7) at each escalating dose. The platelet rich plasma was analyzed for the expression of AKT proximal substrate pSer9 GSK3 β and total GSK3 β . Points represent the levels of pSer9 GSK3 β as a percent of the baseline levels normalized to the levels of total GSK3 β for individual patients and orange lines represent mean of all patients at that time point. **p<0.01; ***p<0.001 Paired t-test compared to baseline.

Figure 2B: Pharmacodynamic profile of capivasertib and olaparib in serially collected PRP during dose expansion on a 2 days on 5 days off schedule.

During the cohort expansion, to enable PD studies on the 2-days-on, 5-days-off schedule, olaparib was administered alone from cycle 0 days -10 to -7, before capivasertib was given alone from cycle 0 days -6 to -3, before both drugs were

given in combination from cycle 1 day 1. PRP was collected from patients at baseline (cycle 0 Day -10), cycle 0 day -5 (post capivasertib only) and cycle 1 day 2 (post capivasertib and olaparib combination). PRP was analyzed for the expression of AKT proximal substrate pSer9 GSK3 β and total GSK3 β . Points represent the levels of pSer9 GSK3 β as a percent of the baseline levels normalized to the levels of total GSK3 β for individual patients and orange lines represent mean of all patients at that time point. *** $p < 0.001$, one-way ANOVA.

Figure 2C-2D: Pharmacodynamic effects of capivasertib and olaparib in paired tumor biopsies during dose expansion on 640mg BID of capivasertib 2-days-on, 5-days-off and 300mg BID of olaparib.

Tumor biopsies were collected from patients at baseline (Pre) and C1D16 (Post). Tumor biopsies were analyzed for the expression of phosphorylated ERK (Figure 1C) and BRCA1 by IHC (Figure 1D).

Figure 3: Antitumor response waterfall and swimmer plots with corresponding patient/tumor characteristics.

Figure 3A. Waterfall plot showing best target lesion response by RECIST 1.1 for patients where this could be evaluated. Red bars represent patients harboring germline *BRCA1/2* mutations, blue bars represent patients with somatic *BRCA1/2* mutations, and grey bars indicate patients who did not have any *BRCA1/2* mutations detected. Co-occurring genomic alterations are listed above the respective bars in responding patients without *BRCA1/2* mutations detected. Hatched bars indicate patients with a tumor marker response (PSA or CA-125) where these data were available.

Figure 3B. Waterfall plot showing best target lesion response by RECIST 1.1 for patients where this could be evaluated. Mutations used to classify tumors into DDR- or PI3K- mutated, or both, are shown below the bars for each patient, along with abbreviated site of the primary tumor. Hatched bars indicate patients with a tumor marker response (PSA or CA-125) where these data were available. Horizontal dotted lines represent RECIST 1.1 thresholds for progression (+20%) and partial response (−30%). Genes with mutations are shown with colored tiles. Tumor + Plasma denotes mutations observed in all samples, i.e. original Tumor and plasma where this was available. Tumor (only) denotes mutation only observed in original tumor sample and absent from subsequent plasma samples. Plasma (only) denotes a mutation observed only in plasma samples and not the original tumor sample. Germline and reversion mutations, as well as PTEN IHC classifications, are shown by symbols as indicated. The middle panel shows genes used to classify the tumors in the waterfall plot, and the lower panel shows other genes of interest.

Figure 3C. Swimmer plot showing time on study for patients, categorized as in Figure 3B.

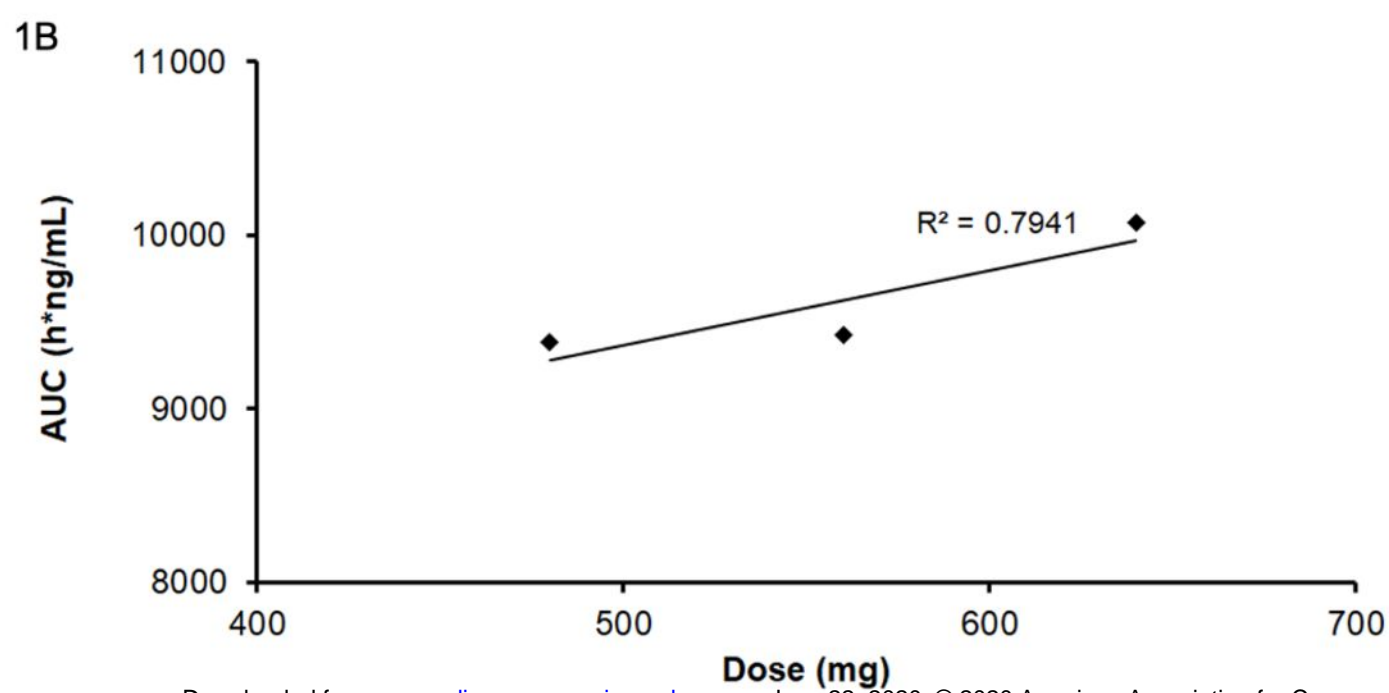
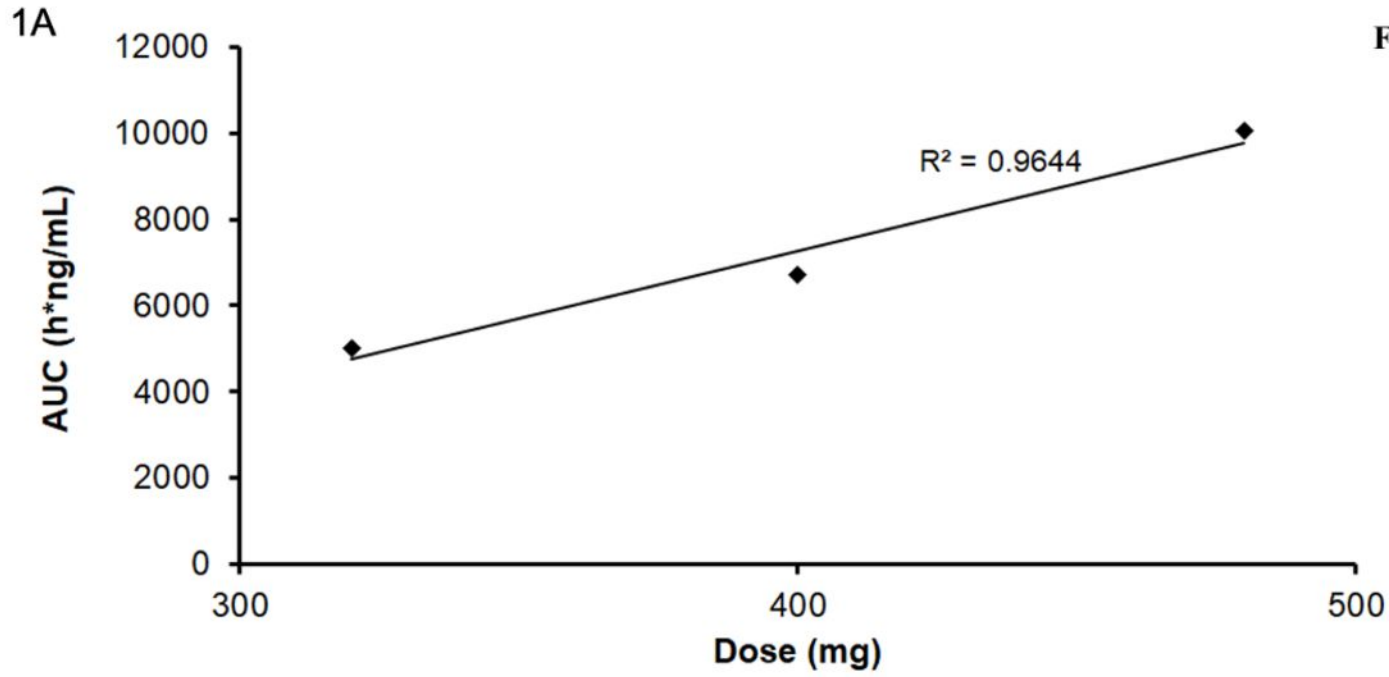


Figure 2

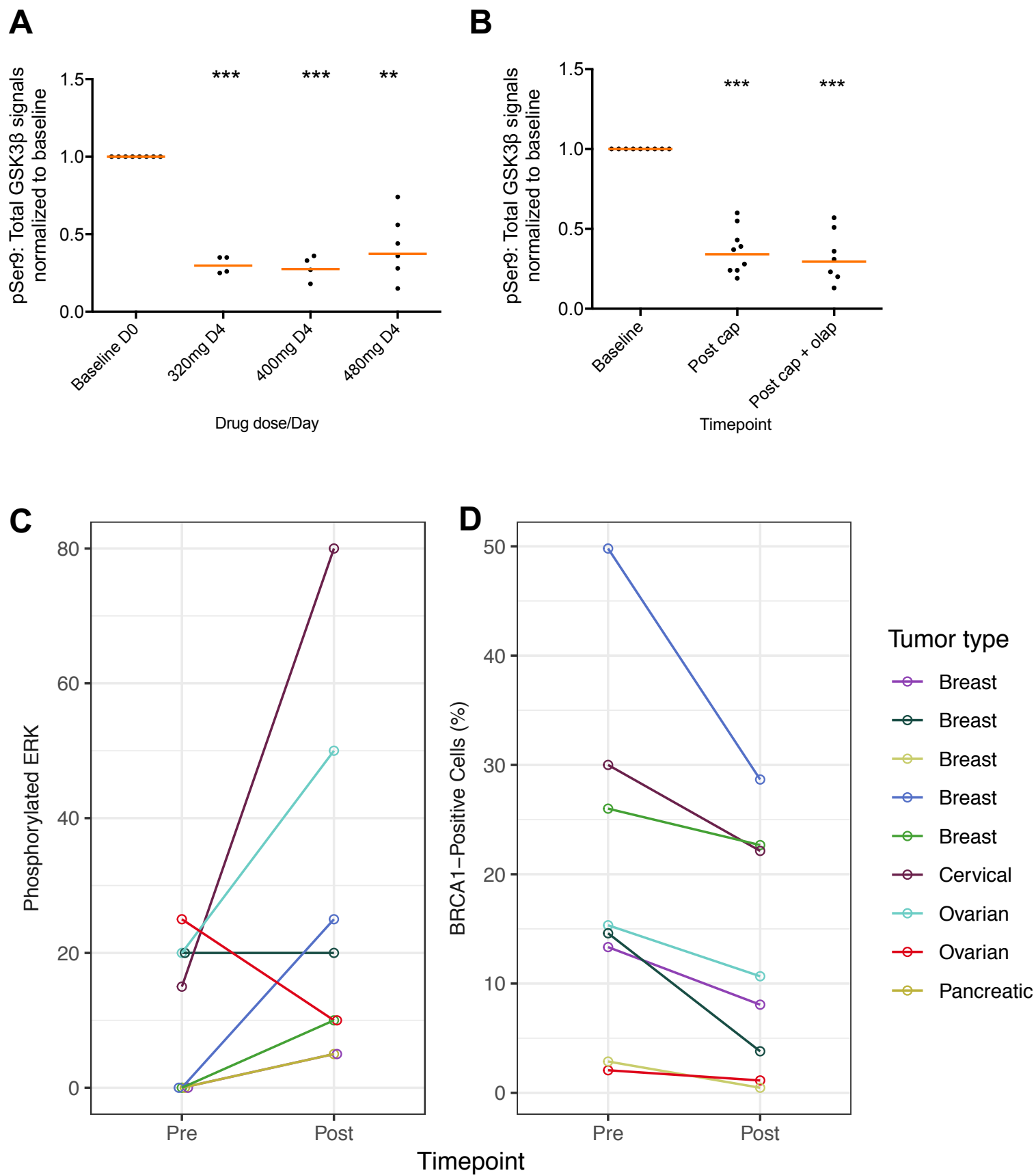
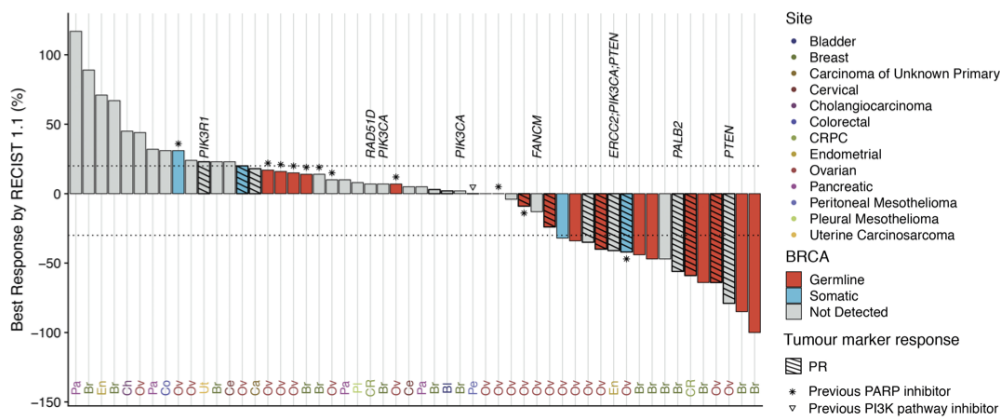
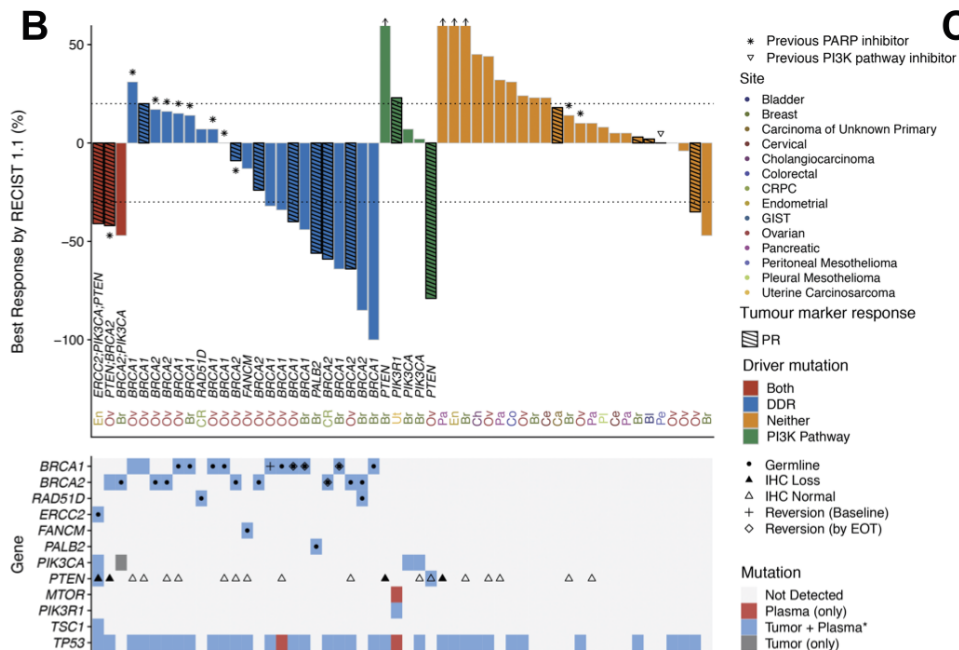


Figure 3

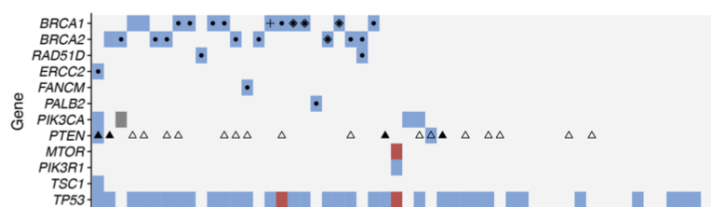
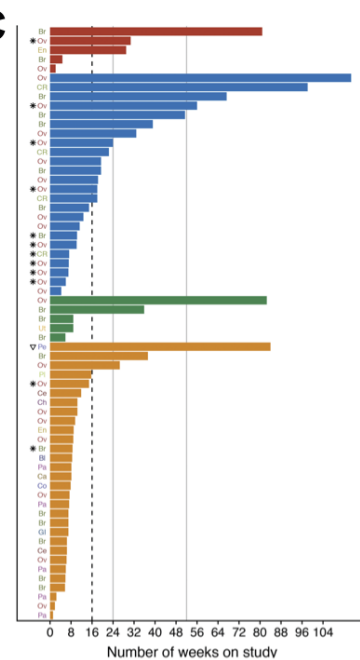
A



B



C



CANCER DISCOVERY

Phase I trial of the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib and AKT inhibitor capivasertib in patients with BRCA1/2 and non-BRCA1/2 mutant cancers

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