Olaparib and α-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial

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Summary

Background Based on preclinical work, we found that combination of poly (ADP-ribose) polymerase (PARP) inhibitors with drugs that inhibit the homologous recombination repair (HRR) pathway (such as PI3K inhibitors) might sensitise HRR-proficient epithelial ovarian cancers to PARP inhibitors. We aimed to assess the safety and identify the recommended phase 2 dose of the PARP inhibitor olaparib in combination with the PI3K inhibitor alpelisib in patients with epithelial ovarian cancer and in patients with breast cancer.

Methods In this multicentre, open-label, phase 1b trial following a 3+3 dose-escalation design, we recruited patients aged 18 years or older with the following key eligibility criteria: confirmed diagnosis of either recurrent ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous histology; confirmed diagnosis of either recurrent ovarian, fallopian tube, or primary peritoneal cancer of any histology with known germline *BRCA* mutations; confirmed diagnosis of recurrent breast cancer of triple-negative histology; or confirmed diagnosis of recurrent breast cancer of any histology with known germline *BRCA* mutations. Additional patients with epithelial ovarian cancer were enrolled in a dose-expansion cohort. Four dose levels were planned: the starting dose level of alpelisib 250 mg once a day plus olaparib 100 mg twice a day (dose level 0); alpelisib 250 mg once a day plus olaparib 200 mg twice a day (dose level 1); alpelisib 300 mg once a day plus olaparib 200 mg twice a day (dose level 2); and alpelisib 200 mg once a day plus olaparib 200 mg twice a day (dose level 3). Both drugs were administered orally, in tablet formulation. The primary objective was to identify the maximum tolerated dose and the recommended phase 2 dose of the combination of alpelisib and olaparib for patients with epithelial ovarian cancer and patients with breast cancer. Analyses included all patients who received at least one dose of the study drugs. The trial is active, but closed to enrolment; follow-up for patients who completed treatment is ongoing. This trial is registered with ClinicalTrials.gov, number NCT01623349.

Findings Between Oct 3, 2014, and Dec 21, 2016, we enrolled 34 patients (28 in the dose-escalation cohort and six in the dose-expansion cohort); two in the dose-escalation cohort were ineligible at the day of scheduled study initiation. Maximum tolerated dose and recommended phase 2 dose were identified as alpelisib 200 mg once a day plus olaparib 200 mg twice a day (dose level 3). Considering all dose levels, the most common treatment-related grade 3–4 adverse events were hyperglycaemia (five [16%] of 32 patients), nausea (three [9%]), and increased alanine aminotransferase concentrations (three [9%]). No treatment-related deaths occurred. Dose-limiting toxic effects included hyperglycaemia and fever with decreased neutrophil count. Of the 28 patients with epithelial ovarian cancer, ten (36%) achieved a partial response and 14 (50%) had stable disease according to Response Evaluation Criteria in Solid Tumors 1.1.

Interpretation Combining alpelisib and olaparib is feasible with no unexpected toxic effects. The observed activity provides preliminary clinical evidence of synergism between olaparib and alpelisib, particularly in epithelial ovarian cancer, and warrants further investigation.

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Introduction

Approximately 50% of high-grade serous ovarian carcinomas harbour genetic or epigenetic alterations in the homologous recombination repair (HRR) pathway.[1] HRR-deficient cancers are sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors and this synthetic lethal interaction has been applied to the treatment of epithelial ovarian cancer. Three PARP inhibitors (olaparib, rucaparib, and niraparib) have received approval from the European Medicines Agency and US Food and Drug

Research in context

Evidence before this study

We searched PubMed for studies published between Jan 1, 2000, and Sept 29, 2018, that explored combinations between poly (ADP-ribose) polymerase (PARP) inhibitors and other drugs in patients with advanced or metastatic cancers, or both. We used the search terms "combination" AND "PARP inhibitor OR olaparib OR niraparib OR rucaparib OR talazoparib OR veliparib" and refined our search to clinical trials. This search revealed several trials exploring combinations of PARP inhibitors with chemotherapy and a few trials exploring combinations of PARP inhibitors with targeted drugs such as cediranib and buparlisib. None of the trials of chemotherapy combinations showed evidence of clinical synergism between the PARP inhibitor and the cytotoxic agent, at least in part because these combinations require attenuation of PARP inhibitor or cytotoxic agent dosing. Similarly, we found no reported evidence of clinical synergism between PARP inhibitors and targeted drugs, at least in tumours that were homologous recombination repair (HRR)-proficient. One previously reported olaparib and cediranib study included only patients with recurrent platinum-sensitive ovarian cancer, a setting enriched for HRR deficiency. Based on preclinical work supporting synergism of PI3K and PARP inhibitors, we initially completed a phase 1b dose-escalation study of the pan-PI3K inhibitor buparlisib and the PARP inhibitor olaparib for the treatment of recurrent ovarian and breast cancer, but CNS toxicity precluded meaningful escalation of buparlisib. To overcome this problem, we assessed the α-specific PI3K inhibitor alpelisib (which has not shown CNS toxicity) in combination with olaparib in a phase 1b study with dose expansion in patients with ovarian cancer.

Added value of this study

This hypothesis-driven, investigator-initiated phase 1b dose-escalation clinical trial of alpelisib and olaparib with dose expansion in patients with ovarian cancer showed that the olaparib and alpelisib combination is feasible and shows clinical evidence of synergism in *BRCA* wild-type (somatic and germline), platinum-resistant ovarian carcinomas (ie, in tumours enriched for HRR proficiency). To our knowledge, this is the first time that clinical evidence of synergism between a PARP inhibitor and a targeted agent or chemotherapy is reported in *BRCA* wild-type, platinum-resistant ovarian cancer. The RECIST 1.1 overall response of olaparib and alpelisib of 33% in these cancers is substantially higher than the overall response expected from olaparib monotherapy (4–5%) or alpelisib monotherapy (<5%) in this setting. Furthermore, this study highlights a novel mechanism of action: use of a PI3K inhibitor to sensitise HRR-proficient ovarian cancers to PARP inhibitors.

Implications of all the available evidence

Our study has shown that the combination of alpelisib and olaparib exhibits synergistic activity in *BRCA* wild-type, platinum-resistant ovarian cancers, thereby expanding potential use of PARP inhibitors beyond the setting of HRR deficiency, for which they currently have approval from the European Medicines Agency and US Food and Drug Administration. Our results and the mechanistic rationale behind PARP and PI3K inhibitor combinations might be applicable not only to *BRCA* wild-type, platinum-resistant ovarian cancers, but also to other solid tumours with or without PI3K pathway alterations, including *BRCA* wild type breast cancer, prostate, colorectal, and endometrial cancers. Additional work in breast cancer might be particularly informative, given the promising results of the phase 3, SOLAR-1 study of alpelisib in combination with fulvestrant in hormone receptor-positive, HER2-negative breast cancer, in which hyperactivation of the PI3K pathway can occur due to *PIK3CA* mutations in around 40% of patients.

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Administration (FDA) as monotherapy either in patients with germline or somatic *BRCA1* or *BRCA2* mutations or as maintenance therapy after platinum chemotherapy in platinum-sensitive recurrent epithelial ovarian cancer.[2–5]

The potential of PARP inhibitors in the management of epithelial ovarian cancer is tempered, however, by the fact that epithelial ovarian cancers with intrinsic, de novo HRR proficiency do not respond as well as HRR-deficient carcinomas.[5,6] Furthermore, the most prevalent mechanism of acquired PARP inhibitor resistance in HRR-deficient cancers is acquisition of HRR proficiency as a consequence of secondary genetic or epigenetic events (such as secondary mutations in *BRCA1*, *BRCA2*, *RAD51C*, or *RAD51D*, or reversal of *BRCA1* promoter methylation) that restore HRR proficiency and confer PARP inhibitor resistance.[2,7–9] Taken together, either de-novo HRR proficiency (present in as many as 50% of high-grade serous ovarian carcinomas) or acquired HRR proficiency (the most important mechanism of PARP inhibitor resistance in HRR-deficient carcinomas) pose a major challenge for the successful use of PARP inhibitors in epithelial ovarian cancer.

Combinations of PARP inhibitors with drugs that inhibit HRR might represent an effective strategy to sensitise epithelial ovarian cancers with de novo or acquired HRR proficiency to PARP inhibitors and potentially expand use of these drugs beyond HRR-deficient epithelial ovarian cancers. Previous work has shown that PI3K inhibition leads to downregulation of *BRCA1* or *BRCA2* and abrogation of HRR, increased DNA damage, gain in poly ADP-ribosylation, and subsequent sensitisation to PARP inhibitors. Importantly, synergism between PI3K and PARP inhibitors is observed both in vitro and in vivo, in HRR-proficient and HRR-deficient models of breast cancer.[10,11] Mechanistically, downregulation of *BRCA1* or *BRCA2* appears to be mediated by ERK-dependent activation of the ETS transcription factor, which suppresses *BRCA1* or *BRCA2* gene transcription, thereby causing a deficiency in HRR

and concomitant PARP inhibitor sensitivity.[10,12] The enhanced DNA damage induced by PI3K inhibitors might also be a consequence of impaired production of nucleotides needed for DNA synthesis and repair.[13] Specifically, PI3K inhibitors disproportionately affect the non-oxidative pentose phosphate pathway that delivers ribose-5-phosphate required for synthesis of ribonucleotides, ultimately leading to a decrease in all four nucleotide triphosphates.[13]

To evaluate the synergism between PI3K and PARP inhibitors in the clinic, we initially did a phase 1b dose-escalation study of the pan-PI3K inhibitor buparlisib (BKM120) and the PARP inhibitor olaparib for the treatment of recurrent ovarian and breast cancer.[14] However, CNS toxic effects (depression observed in 36% of patients and anxiety observed in 28% of patients) and grade 3 transaminase elevation prevented meaningful dose escalation of buparlisib. Not unexpectedly, in that study the anticancer activity of olaparib and buparlisib in patients with epithelial ovarian cancer (70% of whom harboured germline *BRCA* mutations) was similar to the historical activity of olaparib monotherapy in that population—ie, there was no evidence that addition of buparlisib at the doses administered contributed any additional activity to olaparib monotherapy. To overcome the problem of toxic effects on the CNS and transaminase abnormalities and to continue the search for preliminary clinical evidence of synergism between PI3K and PARP inhibitors, we have now evaluated the α-specific PI3K inhibitor alpelisib (BYL719) in combination with olaparib in a phase 1b study for patients with epithelial ovarian cancer. Alpelisib has not shown CNS toxic effects and showed promising results in combination with endocrine therapy (fulvestrant) for hormone receptor-positive, HER2-negative breast cancer with *PIK3CA* mutations in the phase 3 SOLAR-1 study.[15]

Methods

Study design and participants

See Online for appendix

In this multicentre, open-label, phase 1b trial following a 3+3 dose-escalation design, we recruited patients with the following key eligibility criteria: confirmed diagnosis of either recurrent ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous histology; confirmed diagnosis of either recurrent ovarian, fallopian tube, or primary peritoneal cancer of any histology with known germline *BRCA* mutations; confirmed diagnosis of recurrent breast cancer of triple-negative histology; or confirmed diagnosis of recurrent breast cancer of any histology with known germline *BRCA* mutations. Other inclusion criteria were age 18 years or older, Eastern Cooperative Oncology Group performance status of 1 or lower, estimated life expectancy of greater than 4 months, adequate bone marrow function (haemoglobin >9·0 g/dL, absolute neutrophil count >1500 cells per μL, and platelet count >100 000 platelets per μL), adequate liver function (total bilirubin concentration <upper limit of normal [ULN], alanine and aspartate aminotransferase concentration <2·5×ULN [<5×ULN for patients with liver metastases], prothrombin time international normalised ratio <1·5), adequate kidney function (serum creatinine concentration <ULN or calculated creatinine clearance ≥35 mL/min using Cockcroft-Gault formula), fasting serum amylase ≤2×institutional ULN, fasting serum lipase ≤institutional ULN, and both fasting plasma glucose ≤140 mg/dL (7·7 mmol/L) and glycated haemoglobin ≤6·4% (47 mmol/mol). Patients also had to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria or CA 125-evaluable cancer by Gynecological Cancer Intergroup criteria. Exclusion criteria were major comorbidities, including myocardial infarction within the previous 6 months, impairment of gastrointestinal function, gastrointestinal disease that might substantially alter the absorption of oral drugs, ongoing or active infection, acute or chronic liver disease, renal disease, lung disease, pancreatitis, psychiatric illnesses, or social situations that would reduce compliance with study requirements. There was no line limit on previous therapies; patients with recurrent, metastatic, triple-negative breast cancer must have had at least one chemotherapy regimen for metastatic breast cancer or have developed metastatic breast cancer within 1 year of completion of adjuvant chemotherapy. Previous therapy for platinum-sensitive patients with ovarian carcinoma must have included two platinum-based chemotherapy regimens. Platinum-sensitive, resistant, or refractory disease was allowed. Platinum-refractory disease was defined either as relapse less than 2 months after the last platinum-based chemotherapy or relapse during platinum-based chemotherapy. Platinum resistance was defined as relapse within 2 to 6 months after the last dose of platinum-based chemotherapy. Platinum sensitivity was defined as relapse more than 6 months after the last dose of platinum-based chemotherapy. Previous use of PARP and PI3K inhibitors was allowed for patients in the dose-escalation cohort but not for patients in the dose-expansion cohort. The full list of inclusion and exclusion criteria is in the appendix (pp 63–70).

The clinical trial was approved by the institutional review boards of all participating institutions and by the FDA. All procedures involving human participants were carried out in accordance with the Declaration of Helsinki. Written, informed consent was obtained from patients or guardians before enrolment in the study.

Procedures

Oral olaparib was administered twice daily (in tablet formulation) and oral alpelisib once daily (in tablet formulation) on a 28-day cycle. Four dose levels were planned: starting dose level alpelisib 250 mg once a day plus olaparib 100 mg twice a day (dose level 0); alpelisib 250 mg once a day plus olaparib 200 mg twice a day (dose level 1); alpelisib 300 mg once a day plus olaparib 200 mg twice a day (dose level 2); and alpelisib 200 mg once a day

plus olaparib 200 mg twice a day (dose level 3). Treatment continued indefinitely until progression, unacceptable toxicity, patient refusal, intercurrent illness that prevented further administration of treatment, or general or specific changes in the participant's condition that rendered the participant ineligible for further treatment according to the treating investigator. Dose modifications and reductions followed prespecified rules (appendix pp 94–129). Generally, adverse events worse than grade 2 delayed administration of the study drug until toxicity resolved to grade 1 or lower; both study drugs would be delayed in cycle 1, and the drug deemed to be the cause of the adverse event would be delayed in cycle 2 and beyond. If adverse events resolved to grade 1 or lower within 7 days, drugs were resumed at the same dose level, but if adverse events resolved to grade 1 or lower within 8–28 days, protocol treatment was restarted at the next lowest dose of drug causing the toxic effect. If the toxic effects did not resolve within 28 days, participants were removed from the study. Similar criteria were followed if the patients developed a dose-limiting toxic effect. Intrapatient dose escalation was allowed if agreed with the treating physician and principal investigator (appendix p 75).

Tumour assessment by RECIST 1.1 occurred every 8 weeks (two cycles) and included assessment of chest, abdomen, and pelvis via CT or MRI scan. After completion of cycle 16, tumour assessment was done every 12 weeks. Blood samples for pharmacokinetics analysis were taken for alpelisib and olaparib immediately after dosing of both drugs on day 1 and then on days 8 and 15 of cycle 1 at 0 h, 1 h, 2 h, 4 h, and 8 h after dosing of both drugs. Toxic effects were monitored weekly during cycles 1 and 2 and then at day 1 of each cycle by means of both blood tests and clinical examination. Toxicity was assessed by Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. A dose-limiting toxic effect was defined as a treatment-related toxic effect occurring during the first 4 weeks of treatment, and included any grade 3 or 4 non-haematological event (excluding fatigue, nausea, vomiting, constipation, diarrhoea, electrolyte imbalances, rash that resolved to grade 2 or lower within a maximum of 5 days, or grade 3 hypertension controlled with antihypertensive therapy); any grade haematological events (including grade 4 neutropenia of at least 7 days, febrile neutropenia, grade 4 thrombocytopenia, bleeding with grade 3 thrombocytopenia, and requirement for repeated blood transfusion within 4–6 weeks); inability to take 75% or more of the planned dose; any grade 5 event related to study treatment; and any grade 3 or 4 event considered dose-limiting.

Tumour DNA from archival, formalin-fixed tissues was analysed at the Dana-Farber Cancer Institute (Boston, MA, USA) with the OncoPanel targeted next-generation sequencing test (Dana-Farber Cancer Institute, Boston, USA). The Clinical Laboratory Improvement Amendments-approved OncoPanel test covers exons of over 300 cancer-associated genes, plus intronic regions of genes involved in somatic rearrangements. OncoPanel tests are reviewed by molecular pathologists and report mutations, insertion-deletions, copy number variations, and structural variants in the targeted genes.[16–18]

Outcomes

The primary objective of this study was to identify the maximum tolerated dose and the recommended phase 2 dose of the combination of alpelisib and olaparib for patients with epithelial ovarian cancer and patients with breast cancer. Secondary objectives were safety, observed toxic effects, pharmacokinetics, and preliminary activity of olaparib and alpelisib as assessed as the proportion of patients achieving an overall response according to RECIST 1.1.

At each radiological assessment, stable disease was defined by RECIST 1.1 as neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of tumour diameters. RECIST 1.1 criteria only require confirmation when the overall response is the primary endpoint, so in this phase 1b study the schedule of assessments by protocol did not require a confirmatory scan or independent radiological review. Best overall response was defined as stable disease if a partial response was not observed on treatment and if criteria for progression were not met at the first restaging. Restaging occurred at tumour assessment every 8 weeks. Duration of stable disease was dichotomised at 6 months (ie, stable disease at <6 months vs at ≥6 months).

Duration of response and progression-free survival were prespecified exploratory endpoints that were included and defined in the protocol (appendix pp 144–50). Duration of response was measured from the date of overall response to the date of documented disease progression or removal from treatment, whichever occurred first. Progression-free survival was defined as the time in months from registration to documented disease progression (per RECIST 1.1), clinical progression, or death from any cause, whichever occurred first.

All patients were followed up for overall survival (appendix p 93, pp 140–41). Exploratory correlative endpoints were preliminary evidence of olaparib and alpelisib activity in patients with and without germline *BRCA* mutations, somatic *BRCA* mutations, or both; olaparib and alpelisib activity in patients with platinum-resistant or refractory disease; and olaparib and alpelisib activity in molecularly defined subgroups of patients with or without HRR and PI3K pathway alterations as identified by the OncoPanel assay. Measurement of olaparib and alpelisib activity in patients with and without germline and somatic *BRCA* mutations was prespecified; overall survival and olaparib and alpelisib activity in subgroups of patients with other mutations identified in the OncoPanel (such as HRR and PI3K pathway alterations) were assessed post hoc.

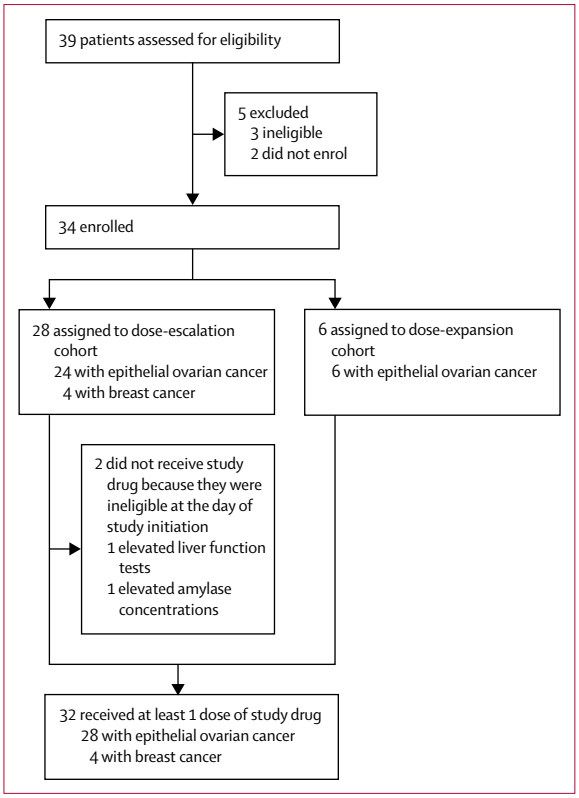

Figure 1: **Trial profile**

	Patients with epithelial ovarian cancer (n=28)	Patients with breast cancer (n=4)
Gender		
Female	28 (100%)	4 (100%)
Male	0	0
Age, years	60 (55–67)	46·5 (33–64)*
Ethnicity		
Non-Hispanic	23 (82%)	4 (100%)
Not reported	5 (18%)	0
Race		
White	25 (89%)	3 (75%)
Other	3 (11%)	1 (25%)
Germline *BRCA* mutation status		
Unknown	1 (4%)	1 (25%)
Pathogenic mutation	10 (36%)	2 (50%)
Wild type	17 (61%)	1 (25%)
Platinum status		
Platinum resistant	23 (82%)	..
Platinum sensitive	2 (7%)	..
Platinum refractory	3 (11%)	..
Carcinoma type		
Ovarian	26 (93%)	..
Primary peritoneal	2 (7%)	..
Cancer stage at diagnosis		
IIA	0	2 (50%)
IIB	2 (7%)	0
IIC	2 (7%)	0
IIIB	0	1 (25%)
IIIC	16 (57%)	0
IV	8 (29%)	1 (25%)
Histology		
High-grade papillary serous carcinoma	21 (75%)	..
Poorly differentiated adenocarcinoma not otherwise specified	5 (18%)	..
Carcinosarcoma	1 (4%)	..
Mixed high-grade serous and transitional cell carcinoma	1 (4%)	..
Invasive ductal carcinoma	..	1 (25%)
Metaplastic carcinoma	..	1 (25%)
Lines of previous therapy	3 (2–5)	3·8 (2–5)*

Data are n (%) or median (IQR). *Mean (range).

Table 1: **Baseline characteristics**

Statistical analysis

We designed this clinical trial as a 3+3 dose-escalation study, with dose escalation if none of three or one of six participants had a dose-limiting toxic effect during the first 28-day cycle of therapy. If the true rate of dose-limiting toxic effects is 30% in this disease setting, the conventional probability of dose escalation is 0·49. The monotonic dose–efficacy relationship for olaparib has been well established,[19] and similar monotonic dose–efficacy relationships for alpelisib[20] and other PI3K inhibitors[21] have been documented. Additionally, given our hypothesis (based on our preclinical work) that the synergism between PARP and PI3K inhibitors depends on inhibition of the PI3K pathway (which is dose dependent), we predicted a monotonic efficacy for the combination of olaparib and alpelisib. Once the maximum tolerated dose was established, six patients with epithelial ovarian cancer were enrolled into a dose-expansion cohort to further define the safety and tolerability of the recommended phase 2 dose and to measure secondary objectives including preliminary activity of the combination and translational endpoints. We assessed safety and efficacy in all patients who received at least one dose of either of the study drugs.

Progression-free survival, duration of response, and overall survival analyses were summarised with the Kaplan-Meier product limit estimator. 95% CIs were reported for outcome events (such as progression for progression-free survival, or death for overall survival) at landmark times and for median progression-free and overall survival using Greenwood's formula. The association of patient and disease characteristics with

overall response was explored using Fisher's exact tests (significance threshold p<0·05). Patient demographics and adverse event frequencies were summarised with descriptive statistics. All statistical analyses were done with R (version 3.4.4). This study is registered with ClinicalTrials.gov, number NCT01623349.

Role of the funding source

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

Results

Between Oct 3, 2014, and Dec 21, 2016, we enrolled 34 patients from six hospitals in the USA (appendix, p 6): 28 in the dose-escalation cohort and six in the dose-expansion cohort (figure 1). 30 patients had epithelial ovarian cancer (24 in the dose-escalation cohort and six in the dose-expansion cohort). Four patients had breast cancer, all in the dose-escalation cohort. Two patients with epithelial ovarian cancer in the dose-escalation cohort did not receive study treatment because they were deemed ineligible for the study and therefore are excluded from all analyses. At the time of data cutoff (Feb 15, 2018) only two patients with epithelial ovarian cancer remained on protocol treatment, with a median follow-up of 12 months (IQR 8–17). The baseline characteristics of the 28 patients with epithelial ovarian cancer are summarised in table 1; ten (36%) were positive for pathogenic germline *BRCA* mutations and 26 (93%) had platinum-resistant or refractory disease. Patients had received a median number of 3 (IQR 2–5) lines of therapy. The preclinical evaluation of this trial, including tolerability and efficacy experiments in xenograft models of ovarian cancer, proof-of-mechanism studies, and target engagement studies are presented in detail in the appendix (pp 9–15).

Of the four dose levels evaluated (table 2), dose level 0 was well tolerated without dose-limiting toxic effects. Patients given dose level 1 had no dose-limiting toxic effects, but most patients had to reduce the alpelisib dose from 250 mg to 200 mg once a day after the 4-week toxic effect determination period had passed. Of the six patients on dose level 2, only two had dose-limiting toxic effects: one had grade 4 hyperglycaemia and one had grade 4 neutropenia and fever. The alpelisib dose was reduced to dose level 1, but this dose level was also associated with two dose-limiting toxic effects (grade 3 hyperglycaemia and inability to take more than 75% of study drug dose). This observation prompted de-escalation of alpelisib to 200 mg once a day (dose level 3). Dose level 3 was associated with one dose-limiting toxic effect (grade 3 hyperglycaemia) in six patients and was deemed safe and selected as the maximum tolerated dose; the six patients with epithelial

	Alpelisib dose (once a day)	Olaparib dose (twice a day)	Patients with ovarian cancer	Patients with breast cancer	Dose-limiting toxicities
Dose level 0 (n=5)	250 mg	100 mg	5	0	0
Dose level 1 (n=4)	250 mg	200 mg	3	1	0
Dose level 2 (n=6)	300 mg	200 mg	4	2	2
Dose level 1 (n=7)	250 mg	200 mg	7	0	2
Dose level 3 (n=6)	200 mg	200 mg	5	1	1
Ovarian cancer dose-expansion cohort at dose level 3 (n=6)	200 mg	200 mg	6	0	NA

28 patients were in the dose-escalation cohort and six in the dose-expansion cohort. Dose-limiting toxicities were not formally assessed in the dose-expansion cohort.

Table 2: **Patients and dose-limiting toxicities at each dose level, presented in the order they were tested**

	Grade 1–2	Grade 3	Grade 4
Nausea	23 (72%)	3 (9%)	0
Hyperglycaemia	17 (53%)	3 (9%)	2 (6%)
Fatigue	18 (56%)	2 (6%)	0
Diarrhoea	16 (50%)	0	0
Vomiting	14 (44%)	2 (6%)	0
Anorexia	10 (31%)	0	0
Headache	8 (25%)	0	0
Anaemia	7 (22%)	0	0
Constipation	5 (16%)	0	0
Increased creatinine	5 (16%)	0	0
Thrombocytopenia	5 (16%)	0	0
Acneiform rash	4 (13%)	1 (3%)	0
Maculopapular rash	4 (13%)	1 (3%)	0
Increased serum amylase	4 (13%)	1 (3%)	0
Abdominal pain	4 (13%)	0	0
Increased alanine aminotransferase	1 (3%)	3 (9%)	0
Dry skin	4 (13%)	0	0
Dysgeusia	4 (13%)	0	0
Dyspnoea	4 (13%)	0	0
Increased lipase	2 (6%)	2 (6%)	0
Mucositis oral	4 (13%)	0	0
Other (weight changes, increased lactate dehydrogenase)	2 (6%)	0	0
Increased aspartate aminotransferase	1 (3%)	1 (3%)	1 (3%)
Febrile neutropenia	0	0	1 (3%)
Increased gamma-glutamyl transferase	0	1 (3%)	0
Pain	0	1 (3%)	0
Rectal pain	0	1 (3%)	0
Renal insufficiency	0	0	1 (3%)

Data are n (%). Grade 1–2 adverse events occurring in at least 10% of all patients and all grade 3 or 4 adverse events are presented (n=32). No grade 5 adverse events were reported.

Table 3: **Treatment-related adverse events**

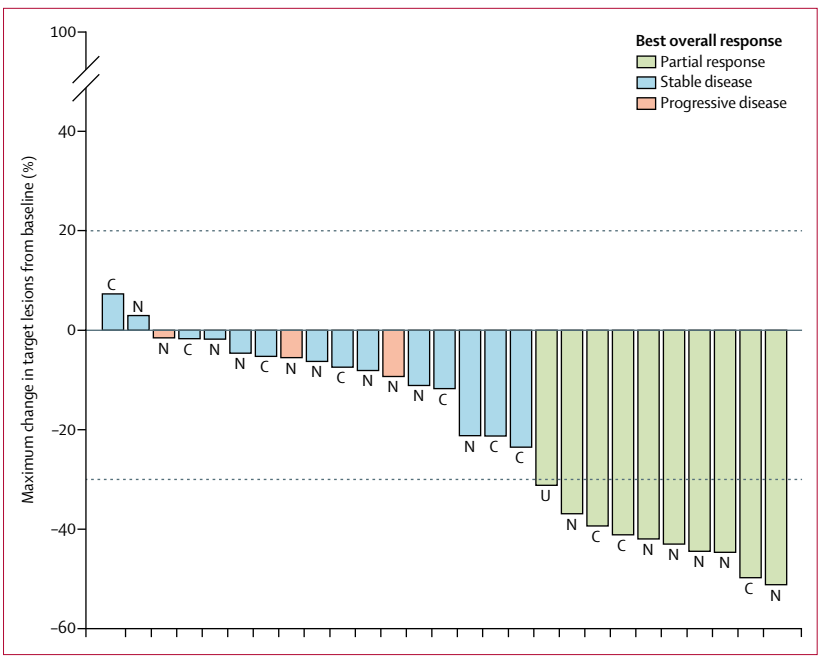

Figure 2: **Response of patients with epithelial ovarian cancer by germline *BRCA* mutation status**
Lesion size was measured in 27 patients with epithelial ovarian cancer. The change in target lesion from baseline is the maximum reduction of target lesion size. Germline *BRCA* mutation status is indicated as C for carrier, N for non-carrier, and U for unknown.

	Germline *BRCA* mutation carrier (n=10)	Germline *BRCA* mutation non-carrier (n=17)	Germline *BRCA* mutation status unknown (n=1)	All patients (n=28)
Partial response	3 (30%)	6 (35%)	1 (100%)	10 (36%)
Stable disease	7 (70%)	7 (41%)	0	14 (50%)
Progressive disease	0	3 (18%)	0	3 (11%)
Unevaluable	0	1 (6%)	0	1 (4%)

Data are n (%).

Table 4: **Best overall response of patients with epithelial ovarian cancer by germline *BRCA* mutation status**

ovarian cancer in the dose-expansion cohort were treated at this dose level. The maximum grades of hyperglycaemia by dose level are presented in the appendix (p 1).

Treatment-related adverse events that were grade 3 or worse or grade 1–2 and occurred in at least 10% of all patients are presented in table 3. There were no unexpected or irreversible toxic effects observed (based on the known toxic effects of olaparib and alpelisib). Unlike buparlisib, CNS adverse events (eg, depression and anxiety) are not a known safety issue with alpelisib, and no CNS events worse than grade 1 were recorded in the study. Nausea, hyperglycaemia (an expected toxic effect of PI3K inhibitors), and fatigue were the most common toxic effects, and were mostly grades 1 and 2. Considering all dose levels, the most common treatment-related grade 3–4 adverse events were hyperglycaemia (five [16%] of 32 patients), nausea (three [9%]), and increased alanine aminotransferase concentrations (three [9%]). Grade 3 transaminase elevations, also a known toxic effect of PI3K inhibitors, were reported in four (13%) of 32 patients (three [9%] had increased alanine aminotransferase concentrations and one [3%] had increased aspartate aminotransferase concentrations). One patient (3%) had grade 4 increased aspartate aminotransferase elevation. Four (13%) patients had lipase elevations (two [6%] were grade 3 elevations), which were reversible. Anaemia was observed in seven (22%) patients and thrombocytopenia was observed in five (16%) patients; both are expected toxic effects of olaparib and all were grade 1–2. Details on patients needing dose reduction per dose level are in the appendix (p 4). Three patients discontinued therapy for drug-related toxic effects, two for grade 3 and grade 4 hyperglycaemia and one for grade 2 nausea and vomiting. Serious adverse events (defined in the study protocol; appendix p 151) included grade 4 hyperglycaemia in two patients, grade 4 febrile neutropenia in one patient, grade 2 hypothyroidism in one patient, and a grade 2 small bowel fistula in one patient. There were no treatment-related deaths; furthermore, no deaths were observed while on protocol treatment.

Pharmacokinetic results for alpelisib and olaparib are in the appendix (pp 2–3). Steady-state C_{max} values measured on day 8, 2 h after dosing for both olaparib and alpelisib, appear similar to C_{max} values obtained when these drugs were tested as monotherapy in the phase 1 setting,[14] with drug exposures increasing proportionally with increasing dose. Alpelisib C_{max} results were unaffected by olaparib dosing, and olaparib C_{max} results appeared unaffected by alpelisib dosing (appendix pp 2–3).

Of the 28 patients with epithelial ovarian cancer included in the analysis, ten (36%) had a partial response, 14 (50%) had stable disease, three (11%) had progressive disease, and one (4%) was unevaluable for best overall response using RECIST 1.1 (figure 2). Of the 14 patients with stable disease, eight (29%) had stable disease for at least 6 months. Of the four patients with breast cancer in the dose-escalation cohort, three had stable disease for three, ten, and 12 cycles, and one patient was removed from protocol treatment before the first cycle (this was the patient with the dose-limiting toxic effect of grade 3 hyperglycaemia at dose level 3).

The proportion of patients with epithelial ovarian cancer who had an overall response (complete or partial response) was similar for patients with germline *BRCA* mutations (30%) and patients with germline *BRCA* wild type (35%; Fisher's exact test p=0·42; table 4). Nine (90%) of ten patients with germline *BRCA* mutations and 16 (94%) of 17 patients with germline *BRCA* wild type had platinum-resistant or refractory disease. The proportion of patients with an overall response was 33% (95% CI 7–70; three of nine patients) in patients with germline *BRCA* mutations who had platinum-resistant or

refractory disease and 31% (95% CI 11–59; five of 16 patients) in those with germline *BRCA* wild type who had platinum-resistant or refractory disease. Eight (80%) of ten patients with partial responses progressed while on treatment and two (20%) discontinued treatment because of intolerability. Best overall response by initial dose level is presented in the appendix (p 4). Median duration of response was 5·5 months (IQR 2·2–6·8; figure 3). A total of 23 progression-free survival events were reported, with a median progression-free survival of 7·2 months (95% CI 4·9–9·0; appendix p 7). 11 patients have died, with a median overall survival of 21·3 months (95% CI 11·4–23·7; appendix p 7). Kaplan-Meier curves of progression-free survival and overall survival by germline *BRCA* mutation status are presented in the appendix (p 8).

In exploratory analyses, tumour DNA of 25 patients with epithelial ovarian cancer was analysed from archival, formalin-fixed tissues (figure 4; appendix p 5). Ten (40%) of 25 patients had germline *BRCA* mutations; of the remaining 15 patients, three (12%) had tumours with somatic *BRCA* mutations (all *BRCA2* mutations); one of the patients with somatic *BRCA* mutations had an overall response (partial response; figure 4). 33% (95% CI 10–65; four of 12 patients) of patients who had *BRCA* wild type (germline and somatic) achieved an overall response; all these patients had platinum-resistant or refractory tumours. Based on the exploratory OncoPanel analysis, six patients had somatic mutations involving HRR genes (three patients had *BRCA2* somatic mutations and three patients had somatic mutations involving only the PI3K pathway) and six patients did not have any somatic mutations in the HRR or PIK3CA pathways (figure 4). Overall responses were seen across all these patient subgroups; specifically, partial responses were recorded in two (33%) of six patients with somatic HRR mutations, one (33%) of three patients with only PI3K pathway mutations, and two (33%) of six patients without HRR and PI3K mutations including one patient with platinum-refractory disease who had received five previous lines of therapy (figure 4).

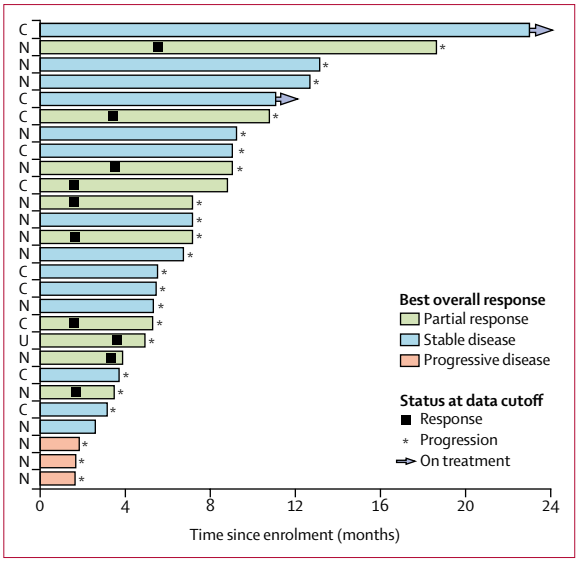

Figure 3: **Duration of response and time to progression**
Summary of the duration of response for the ten patients who achieved partial response and time to progression in the 18 patients who did not achieve a partial response, by germline *BRCA* mutation carrier status and response. Duration of response and time to progression were defined as the interval from date of enrollment to date of either progression or date of last disease assessment. At the time of cutoff, only two patients with epithelial ovarian cancer remained on protocol treatment. Germline *BRCA* mutation status is indicated as C for carrier, N for non-carrier, and U for unknown.

Discussion

This phase 1b dose-escalation study showed that combining alpelisib and olaparib produced no unexpected toxic effects or safety signals and determined the maximum tolerated dose to be alpelisib 200 mg once a day with olaparib 200 mg twice a day, which we consider the recommended phase 2 dose. However, this recommended dose is merely one candidate dose from a number of dose combinations, and the anti-tumour activity data across different doses with similar dose-limiting toxic effects (ie, across dose levels 1 and 3) appear to be consistent (appendix p 4). Adverse events that defined dose-limiting toxic effects included hyperglycaemia and fever with decreased neutrophil count. Regarding hyperglycaemia, our study allowed patients with diabetes mellitus to participate provided their fasting glucose concentration was less than 140 mg/dL (7·7 mmol/L) and their glycated haemoglobin A_{1C} concentrations were less than 6·4%. However, more stringent criteria are currently used in trials of PI3K inhibitors, to decrease the frequency of hyperglycaemia, which is an otherwise expected toxic effect of PI3K inhibitors. Unlike the olaparib and buparlisib study,[14] our study with olaparib and alpelisib had no issues with CNS toxicity (depression and anxiety). Grade 3 or 4 transaminase elevations (another known toxic effect of PI3K inhibitors) were also less frequently observed than for olaparib and buparlisib (16% in this study *vs* 20% for olaparib and buparlisib) and were not dose limiting.[6] Finally, although nausea, fatigue, and vomiting were observed in more than 50% of patients, these toxic effects were mostly grade 1 and 2, easily manageable, and similar to those observed with olaparib monotherapy (77% nausea, 63% fatigue, and 40% vomiting in the recently reported SOLO1 study).[22]

The rationale for the combination of a PI3K inhibitor and a PARP inhibitor was based on the synergy between these two inhibitors observed in animal models of breast cancer.[10,11] The combination of alpelisib and olaparib was further supported by preclinical work in ovarian cancer patient-derived xenograft models (appendix pp 9–15), which showed that alpelisib inhibits HRR and sensitises ovarian cancer models with de novo or acquired HRR proficiency to olaparib.

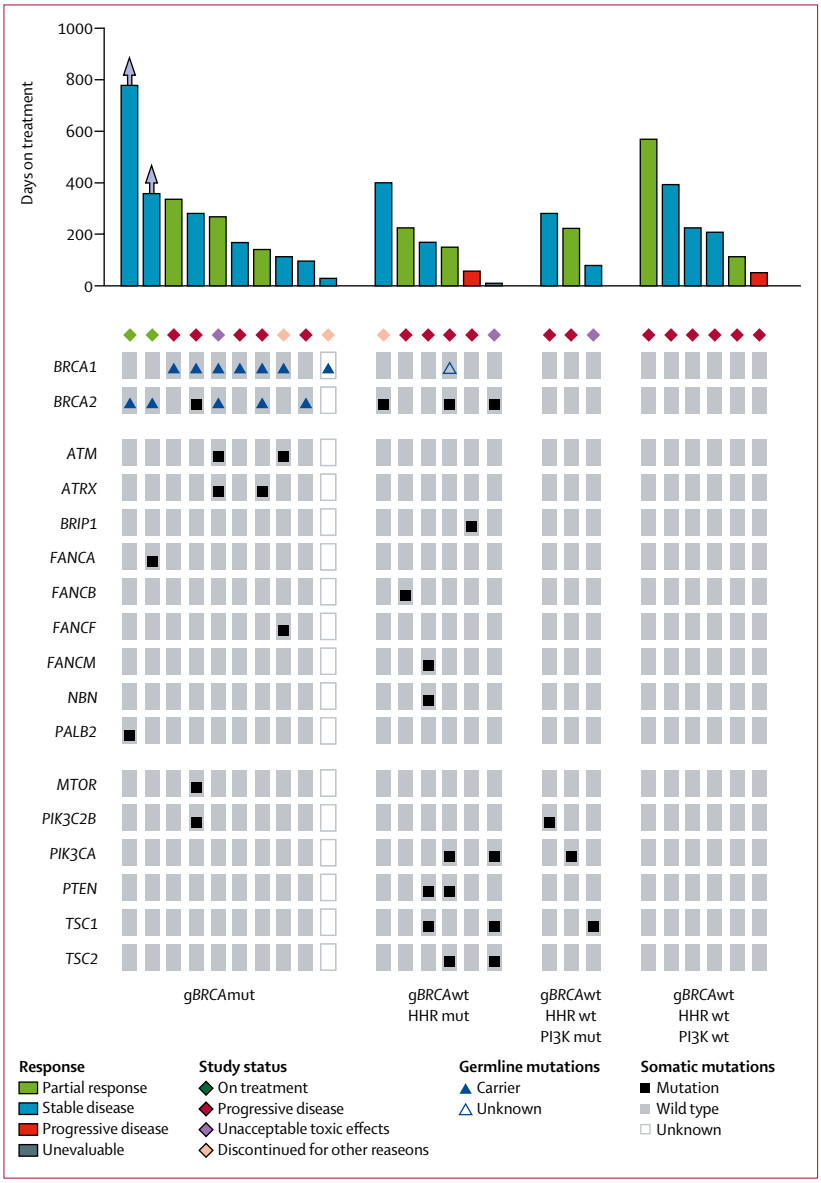

Figure 4: **Genomic aberrations in the HRR and PI3K pathways in 25 patients with epithelial ovarian cancer**
Genes *ATM* to *PALB2* are HRR pathway genes. Genes *MTOR* to *TSC2* are PI3K pathway genes. Mutations were identified through targeted next-generation sequencing. HRR=homologous recombination repair. mut=mutation. wt=wild type.

In the previously published olaparib and buparlisib trial[14] 29% of patients with germline *BRCA* mutations and 12% of patients with germline *BRCA* wild type achieved an overall response. This response was similar to the expected response of olaparib monotherapy in patients with epithelial ovarian cancer who had germline *BRCA* mutations (eg, ≥60% in platinum-sensitive populations and 28% in platinum-resistant populations)[3,6] and germline *BRCA* wild type (eg, 50% in platinum-sensitive populations and at least 5% in platinum-resistant populations).[3,6] These data suggest that buparlisib does not enhance the activity of olaparib monotherapy. This apparent lack of clinical synergism between olaparib and buparlisib study might have been at least partly related to the CNS toxicity precluding dose escalation of buparlisib.

In the olaparib and buparlisib trial,[14] 70% of patients with epithelial ovarian cancer had germline *BRCA* mutations. In this study, 61% of patients with epithelial ovarian cancer had germline *BRCA* wild type and 93% of patients were platinum-resistant or refractory—reflecting a population of patients with epithelial ovarian cancer tumours that were highly enriched for de novo and acquired HRR proficiency. This population of patients gave us the unique opportunity to obtain some preliminary clinical evidence that alpelisib might sensitise HRR-proficient epithelial ovarian cancer to olaparib, which was consistent with the mechanistic rationale behind this study. Notably, we observed an overall response of 31% in germline *BRCA* wild type platinum-resistant patients, and 33% in (germline and somatic) *BRCA* wild type platinum-resistant patients, when the overall response of olaparib and other PARP inhibitors as monotherapy is only around 5%.[3,5,6,23–25] Olaparib as monotherapy was recently discontinued in a large randomised trial (NCT02502266) with patients who had platinum-resistant epithelial ovarian cancer, because of low activity of olaparib in this population. Even in epithelial ovarian cancers that were germline *BRCA* wild type but HRR positive and platinum-resistant, the response to PARP inhibitor niraparib monotherapy in the recently reported QUADRA study[26] was only 10%. Taken together, these previous studies highlight that olaparib and PARP inhibitors in general have minimal activity as monotherapy in these populations, in stark contrast with the preliminary activity of olaparib and alpelisib observed in platinum-resistant epithelial ovarian cancer in this study.

The median duration of response, progression-free survival, and overall survival of patients with platinum-resistant ovarian cancer observed in this population were also promising and in line with the results of the AURELIA study,[27] despite AURELIA allowing a patient population that was substantially less pretreated than in our study (up to two previous lines of therapy, with more than 55% of patients having received only one previous line of therapy). In this study we allowed a median of three previous lines of cytotoxic therapy (without counting previous hormonal therapy and radiotherapy as separate lines) and included patients with as many as eight previous lines of therapy.

When we analysed *BRCA* wild-type tumours for HRR and PI3K pathway alterations, we noted consistent overall responses across all different populations, including two (33%) of six patients without any HRR and PI3K pathway alterations, one of whom had platinum-refractory disease and five previous lines of therapy. It is also important to highlight that PI3K inhibitors as monotherapy have very modest activity in epithelial ovarian cancer.[28,29] Even in epithelial ovarian cancers that have *PIK3CA* mutations, responses are infrequently

seen with PI3K inhibitor monotherapy; in one trial of PI3K inhibitors as monotherapy[30] the overall response in *PIK3CA*-mutated cancers was 0%, with responses observed only with combinations of PI3K inhibitors with other, mainly cytotoxic agents.[30]

The response rate of olaparib and alpelisib was 30% in all patients with germline *BRCA* mutations and 33% in those who also had platinum-resistant disease. This activity is not substantially different to the activity of olaparib alone in this population of patients with ovarian cancer, suggesting that alpelisib does not augment the efficacy of olaparib in the ovarian cancer population with germline *BRCA* mutations. This finding is consistent with the mechanistic rationale behind this study; the synergism between these drugs reflects inhibition of HRR and consequent sensitisation to PARP inhibitors specifically in HRR-proficient tumours, with less synergism expected in tumours enriched for HRR deficiency.

We acknowledge that there are limitations of this study. This was a phase 1b clinical trial, with a small number of patients and with the known limitations of 3 + 3 designs in selecting optimal doses under both toxic effects and biological activity.[31–33] The proportion of patients achieving a response according to RECIST 1.1 was a secondary endpoint with the goal of assessing the preliminary activity of olaparib and alpelisib in combination. We analysed the clinical response in different and distinct subsets of patients to assess whether responses were consistently observed across these subsets, and to assess whether these clinical observations supported our hypothesis (appendix pp 9–15) that alpelisib can sensitise HRR-proficient ovarian cancers to olaparib. The analyses we presented are largely descriptive of the treatment effects and were summarised without a hypothesis test against a null hypothesis. We fully acknowledge that such inferences of patient subsets would require a larger, adequately powered confirmatory study and will be a crucial component of further examination of olaparib and alpelisib in this disease. Nonetheless, our study showed that the combination of alpelisib and olaparib produced no unexpected toxic effects or safety signals, and exhibited preliminary clinical evidence of synergism in *BRCA* wild-type (somatic and germline), platinum-resistant ovarian cancers—ie, in tumours enriched for HRR proficiency. To our knowledge, this is the first time that clinical evidence of synergism between a PI3K and PARP inhibitor is reported for epithelial ovarian cancer. The activity of the olaparib and alpelisib combination in this setting appears to be higher than expected from either olaparib or alpelisib monotherapies, and warrants further investigation.

Contributors

PAK contributed to the study concept, study design, study oversight, data collection, data interpretation, and writing of the manuscript. WTB contributed to the study design, data analysis, data interpretation, creation of figures, and writing of the manuscript. MB, LCC, JL, and MKB contributed to patient recruitment, and to the study concept and study design. CA, RLC, and SNW contributed to the study design and data interpretation, and critically reviewed manuscript drafts. GIS critically reviewed manuscript drafts, and contributed to preclinical and correlative work, data analysis, data interpretation, and manuscript writing. REO'C contributed to patient data collection and data interpretation, and critically reviewed manuscript drafts. CA and RLC contributed to patient data collection. SHK contributed to data interpretation and manuscript writing. JE contributed to preclinical data and data interpretation. JC contributed to data collection. PK contributed to study oversight, data collection, and data interpretation. BK contributed to preclinical and correlative work. SP contributed to preclinical work supporting this study. EW contributed to patient recruitment, study design, and study conception. SF and CW contributed to data collection and data assembly. KAC critically reviewed manuscript drafts, and contributed to data interpretation and patient data collection. ELM contributed to patient recruitment, study design, and study conception. WL reviewed manuscript drafts, and contributed to the study design, data analysis, and data interpretation. GBM contributed to the study concept and to the initiation of the trial. EMS critically reviewed manuscript drafts and contributed to the study design, data collection, data analysis, and data interpretation. ADD'A performed preclinical studies supporting this paper. GMW contributed to the study design, data collection, data analysis, data interpretation, and manuscript writing. UAM contributed to the initial study design, holds the FDA Investigational New Drug application for this study, enrolled patients to this trial, contributed to data collection, data interpretation, and data analysis, and reviewed manuscript drafts. All authors participated in writing the paper and approved the final version of the paper.

Declaration of interests

PAK reports institutional research funding from AstraZeneca and Novartis during the conduct of the study. PAK also reports serving in advisory boards at AstraZeneca, Pfizer, and Merck outside the submitted work. WTB reports institutional research support from Pfizer, outside the submitted work. SNW reports grants and personal fees from AstraZeneca, Clovis, Tesaro, Merck, and Genentech (Roche); grants from Bayer, Cotinga Pharmaceuticals, and Novartis; and personal fees from Pfizer and MediVation, outside the submitted work. KAC reports serving in advisory boards at AstraZeneca and Syndax Pharmaceuticals, outside the submitted work. GIS reports grants and personal fees from Eli Lilly, Pfizer, Merck/EMD Serono, and Sierra Oncology; and personal fees from Roche, Bicycle Therapeutics, Fusion Pharmaceuticals, G1 Therapeutics, Cybrexa Therapeutics, Bayer, Ipsen, Astex, and Almac, outside the submitted work. ELM reports institutional research funding from Pfizer and Myriad. ELM also reports serving as consultant at Eisai, Pfizer, Eli Lilly, and Context Therapeutics. REO'C reports personal fees from Clovis and Tesaro, outside the submitted work. RLC reports grants and personal fees from Genentech (Roche), Clovis, AstraZeneca, Janssen, Oncomed, Novartis, and Genmab; grants from Merck, Abbvie, and Esperance; and personal fees from Tesaro, Agenus, Eisai, Gamamab, and Incyte, outside the submitted work. CA reports personal fees from Tesaro, Immunogen, Clovis, Mateon Therapeutics, and Cerulean Pharma, outside the submitted work. GBM reports grants and personal fees from AstraZeneca, Critical Outcome Technologies, ImmunoMET, Takeda/Millennium Pharmaceuticals, and Pfizer; grants from Adelson Medical Research Foundation, Breast Cancer Research Foundation, Komen Research Foundation, Nanostring, Ovarian Cancer Research Foundation, and Prospect Creek Foundation; personal fees from PDX Pharmaceuticals, Signalchem Lifesciences, Symphogen, Tarveda, and Spindle Top Ventures; and research funding from Ionis and Catena Pharmaceuticals, during the conduct of the study. GBM also has a patent licensed to Nanostring, and a patent licensed to Myriad Genetics. SP reports serving in advisory boards at Elstar Therapeutics outside the submitted work. JL reports personal fees from AstraZeneca, Tesaro, Mersana Therapeutics, and Clovis Oncology, outside the submitted work. LCC is a founder and member of the senior advisory board of Agios Pharmaceuticals and Petra Pharmaceuticals. These companies are developing novel therapies for cancer. His laboratory also receives some financial support from Petra Pharmaceuticals. No drugs from these companies are discussed in this manuscript. SHK reports grants from Stand Up To Cancer during the conduct of the study. EMS reports grants from Stand Up To Cancer during the conduct of the study and personal fees from Johnson & Johnson, outside the submitted work. EW reports personal fees from Genentech (Roche), Infinite MD, Eli

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Data sharing

Upon email request, we would be happy to provide fully de-identified datasets of analyses, including dose-level information for the patients (one record per patient), toxic effects (multiple records per patient), and baseline characteristics and efficacy data for the patients with epithelial ovarian cancer (one record per patient).

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