Efficacy and Safety of Weekly Paclitaxel Plus Vistusertib vs Paclitaxel Alone in Patients With Platinum-Resistant Ovarian High-Grade Serous Carcinoma

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Efficacy and Safety of Weekly Paclitaxel Plus Vistusertib vs Paclitaxel Alone in Patients With Platinum-Resistant Ovarian High-Grade Serous Carcinoma

The OCTOPUS Multicenter, Phase 2, Randomized Clinical Trial

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IMPORTANCE Patients with platinum-resistant or refractory ovarian high-grade serous carcinoma (PR-HGSC) have a poor prognosis and few therapeutic options. Preclinical studies support targeting PI3K/AKT/mTOR signaling in this setting, and a phase 1 study of the dual mTORC1/mTORC2 inhibitor vistusertib with weekly paclitaxel showed activity.

OBJECTIVE To evaluate whether the addition of vistusertib to weekly paclitaxel improves clinical outcomes in patients with PR-HGSC.

DESIGN, SETTING, AND PARTICIPANTS This phase 2, double-blind, placebo-controlled multicenter randomized clinical trial recruited patients from UK cancer centers between January 2016 and March 2018. Patients with PR-HGSC of ovarian, fallopian tube, or primary peritoneal origin and with measurable or evaluable disease (Response Evaluation Criteria in Solid Tumors version 1.1 and/or Gynecological Cancer Intergroup cancer antigen 125 criteria) were eligible. There were no restrictions on number of lines of prior therapy. Data analysis was performed from May 2019 to January 2022.

INTERVENTIONS Patients were randomized (1:1) to weekly paclitaxel (80 mg/m^2 days 1, 8, and 15 of a 28-day cycle) plus oral vistusertib (50 mg twice daily) or placebo.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival in the intention-to-treat population. Secondary end points included response rate, overall survival, and quality of life.

RESULTS A total of 140 patients (median [range] age, 63 [36-86] years; 17.9% with platinum-refractory disease; 53.6% with ≥3 prior therapies) were randomized. In the paclitaxel plus vistusertib vs paclitaxel plus placebo groups, there was no difference in progression-free survival (median, 4.5 vs 4.1 months; hazard ratio [HR], 0.84; 80% CI, 0.67-1.07; 1-sided P = .18), overall survival (median, 9.7 vs 11.1 months; HR, 1.21; 80% CI, 0.91-1.60) or response rate (odds ratio, 0.86; 80% CI, 0.55-1.36). Grade 3 to 4 adverse events were 41.2% (weekly paclitaxel plus vistusertib) vs 36.7% (weekly paclitaxel plus placebo), and there was no difference in quality of life.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of weekly paclitaxel and dual mTORC1/2 inhibition in patients with PR-HGSC, vistusertib did not improve clinical activity of weekly paclitaxel.

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Visual Abstract

Supplemental content

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Despite improvements in first-line treatment for advanced ovarian cancer, approximately 85% of patients experience recurrence and eventually develop fatal chemotherapy resistance. For patients who relapse during ("platinum-refractory") or within 6 months of completing ("platinum-resistant") prior platinum-based therapy, treatment options are limited. Weekly paclitaxel has activity in platinum-resistant ovarian cancer, with objective response rates of approximately 30%. However, the median progression-free survival (PFS) is generally 3 to 4 months, and overall survival (OS), approximately 12 months.[1]

One potential mechanism of resistance to both platinum and taxane chemotherapy is activation of the PI3K/AKT/mTOR signaling pathway.[2-4] Ovarian high-grade serous carcinoma (HGSC) sensitivity to paclitaxel may reflect PI3K pathway activity,[5] potentially driven by *MYC* amplification.[6] However, response rates in single-arm studies of first-generation mTOR inhibitors were poor,[7] which prompted the development of dual mTORC1/2 inhibitors, such as vistusertib. Following encouraging preclinical data in platinum-resistant ovarian cancer xenografts,[5] a phase 1 study of weekly paclitaxel with vistusertib was conducted. The overall response rate was 52% (13 of 25) and median PFS was 5.8 months (95% CI, 3.3-18.5) in the HGSC cohort.[8] Here, we evaluated the clinical efficacy of the vistusertib/paclitaxel combination in OCTOPUS, a multicenter, randomized, placebo-controlled, phase 2 trial in platinum-resistant ovarian HGSC (PR-HGSC).

Key Points

Question Does the addition of the dual mTORC inhibitor vistusertib add benefit to weekly paclitaxel in patients with platinum-resistant ovarian high-grade serous carcinoma (PR-HGSC)?

Findings In this phase 2 randomized clinical trial including 140 patients with PR-HGSC, vistusertib did not increase progression-free survival, overall survival, or response rate when added to weekly paclitaxel.

Meaning The addition of vistusertib to paclitaxel did not improve clinical outcomes in patients with PR-HGSC.

Methods

Study Design

OCTOPUS was a phase 2, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of vistusertib in combination with paclitaxel vs paclitaxel alone in patients with PR-HGSC (trial protocol in Supplement 1). The study was conducted in accordance with the Research Governance Framework for Health and Community Care (second edition; 2006) and the Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2004:1031 and Declaration of Helsinki Principles and was cosponsored by University of Glasgow and NHS Greater Glasgow and Clyde. Ethical approval was obtained from London-Brighton and Sussex Research Ethics Committee (reference 15/LO/1302), and all patients provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Patient Population

Patients (≥18 years) with histologically confirmed HGSC of ovarian, fallopian tube, or primary peritoneal origin with relapse in the platinum-resistant or refractory time frame, were enrolled. Platinum resistant/refractory status was defined as either radiological progression (based on Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]) or cancer antigen 125 (CA-125) rise (according to Gynecological Cancer Intergroup [GCIG] CA-125 criteria) plus symptoms indicative of progression either during (platinum-refractory) or within 6 months of completing (platinum-resistant) prior platinum therapy. Measurable or evaluable disease according to RECIST 1.1 and/or GCIG CA-125 criteria was required.[9] Patients who received weekly paclitaxel in combination with platinum during first-line treatment were eligible if the interval since the last dose of weekly paclitaxel was greater than 6 months at the time of randomization. Patients who received prior weekly paclitaxel for platinum-resistant/refractory disease were excluded. A biopsy was mandatory at study entry if deemed technically feasible. There were no restrictions on number of lines of prior therapy, and the most recent chemotherapy did not have to be platinum-based. See eMethods in Supplement 2 for full inclusion and exclusion criteria.

Study Design, Treatment, and Conduct

A total of 140 participants were randomized (1:1) to receive:

- Weekly paclitaxel plus vistusertib (wP+V): paclitaxel, 80 mg/m^2 intravenously days 1, 8, and 15, plus vistusertib, 50 mg twice daily days 1 to 3, 8 to 10, and 15 to 17 of a 28-day cycle (experimental arm)
- Weekly paclitaxel plus placebo (wP+P): paclitaxel, 80 mg/m^2 intravenously days 1, 8, and 15, plus placebo, twice daily days 1 to 3, 8 to 10, and 15 to 17 of a 28-day cycle (control arm)

After informed consent and eligibility confirmation, participants were allocated to treatment using minimization with a random element and the following stratification factors: treatment center, measurable disease (yes vs no), platinum refractory vs resistant, and taxane-free interval (<6 months vs ≥6 months vs no prior taxane). The inclusion of taxane-free interval as a stratification factor was based on our previous randomized phase 2 trial of weekly paclitaxel in this patient population.[1] Further details of study conduct are detailed in the eMethods in Supplement 2.

Assessments

Imaging assessments (computed tomography of the chest, abdomen, and pelvis or magnetic resonance imaging) were performed at baseline and then every 8 weeks until progression. Measurement of CA-125 was performed every 4 weeks. Post-progression follow-up was performed every 3 months for OS. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.3. Quality of life (QOL) was assessed using

the EuroQol 5-Dimension (EQ-5D) at baseline, prior to each cycle of treatment, end of treatment, and follow-up.

Statistical Analysis

The primary end point was PFS in the intention-to-treat (ITT) population, defined as the time from randomization until the first appearance of confirmed progressive disease as defined by combined RECIST 1.1/GCIG CA-125 criteria[9] or death from any cause. Patients still alive and without progression at the time of analysis were censored at the date last known to be alive and progression free. Secondary end points were response rate (best recorded response according to combined RECIST 1.1 and GCIG CA-125 criteria); OS, defined as the time from randomization until death from any cause; safety and tolerability (according to NCI CTCAE version 4); and QOL as measured by EQ-5D.

The trial followed a 3-outcome design[10]: a PFS difference in favor of wP+V that was statistically significant at 10% was a clear signal that a subsequent phase 3 study is warranted. A result statistically significant at the 20% level (but not 10%) would require supportive data with improved response rate before a subsequent phase 3 would be considered.

A total of 122 PFS events were required to detect a 50% improvement in median PFS from 3.7 months with wP+P to 5.55 months with wP+V with 90% power, at the 20% 1-sided level of statistical significance (or equivalently with 80% power at the 10% level of statistical significance). This required 140 patients (70 patients per arm) recruited over 16.5 months with 8 months of subsequent follow-up. This incorporated an interim analysis for futility, after 40 PFS events had been observed, using a Lan-DeMets spending function[11] and Pocock type boundary.[12]

All analyses were preplanned, unless specified. Efficacy analyses were undertaken on the ITT population, including all patients randomized into the study. Safety and tolerability analyses were undertaken on the safety population, defined as participant who received at least 1 dose of study treatment. The Kaplan-Meier method was used to calculate both PFS and OS. Results were compared using the log-rank test, adjusted for stratification factors, and hazard ratios (HRs) were estimated using the adjusted Cox model. All statistical analyses were performed using SPSS (version 27, IBM), while data were visualized using Prism (version 9.4.1, GraphPad).

Patients' QOL was analyzed using mixed effects and repeated measures models, adjusting for minimization factors, as well as time point and interaction terms (a change from the statistical analysis plan). Both complete case analyses (ignoring missing data) and analyses accounting for missing values using multiple imputation with 40 imputations were undertaken.[13]

Translational Analyses

Assessment of PI3-kinase pathway activity as a predictive biomarker of vistusertib efficacy was a preplanned translational end point, although the methods for assessing pathway activity were not prespecified. Phosphatase and tensin homolog (PTEN) immunohistochemistry (IHC) was quantified using Histo-score (H-score) derived using QuPath. We calculated the median tumor and nontumor H-score for each sample and defined a sample as PTEN high if median tumor H-score was greater than or equal to the corresponding median nontumor H-score as previously[14]; conversely, a sample was classified as PTEN low when median tumor H-score was less than the corresponding median nontumor H-score. We also used DNA ploidy, somatic copy number (CN), and CN signatures as correlates of PI3-kinase pathway activation. Full details of the translational samples and analysis are given in eMethods in Supplement 2.

Results

Patient Demographics

A total of 140 patients (median [range] age, 63 [36-86] years) were randomized (n = 70 vistusertib, n = 70 placebo) from 20 UK sites from January 2016 through March 2018 and constitute the ITT population (**Figure 1**). Baseline characteristics are summarized in the **Table**. Seventy-five (53.6%) patients had received 3 or more prior treatment lines, and 25 (17.9%) were platinum-refractory. Approximately 20% (29 patients) had received prior weekly paclitaxel in combination with carboplatin.

Efficacy

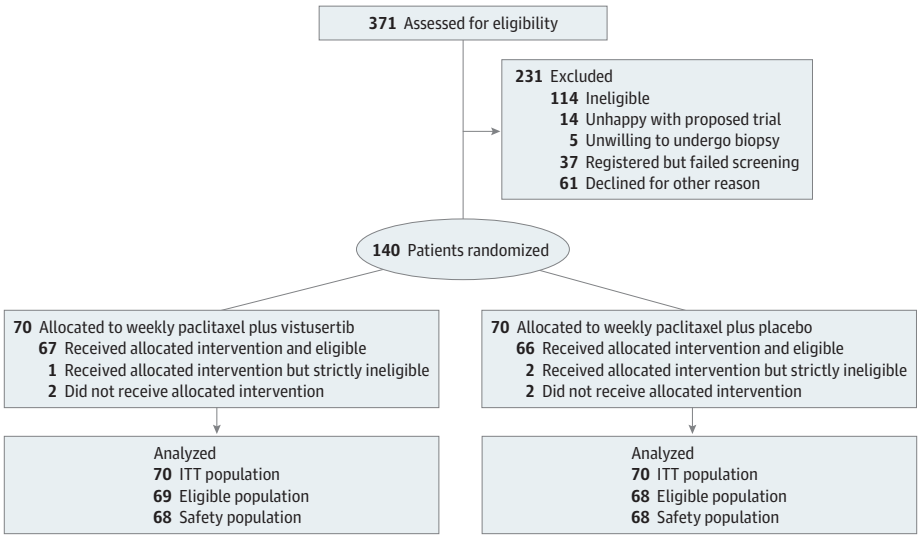
Median PFS was 4.5 vs 4.1 months, and the adjusted HR was 0.84 (80% CI, 0.67-1.07; 1-sided P = .18) for the wP+V arm relative to wP+P arm (**Figure 2**A). Median OS was 9.7 vs 11.1 months (adjusted HR, 1.21; 80% CI, 0.91-1.60) (Figure 2B). Testing of the proportional hazards assumption confirmed that the above HRs from the Cox proportional hazards model are appropriate. Median follow-up for PFS and OS across the whole population was 13.5 and 32.1 months, respectively.

RECIST 1.1 response rates were 29% vs 30% and GCIG combined RECIST 1.1/CA-125 criteria response rates were 53% and 54% for wP+V and wP+P, respectively. There was no difference in response rate by combined GCIG RECIST 1.1/CA-125 criteria (adjusted odds ratio, 0.86; 80% CI, 0.55-1.36). Although PFS was significant at the 20% level, there was no improvement in response rate, and therefore the primary end point was not met as per statistical considerations. There was no difference in PFS or OS according to measurable disease status, platinum status (refractory/resistant), or taxane-free interval (eFigure 1 in Supplement 2).

Tolerability, Treatment Delivery, and QOL

The safety population comprised 136 participants (n = 68 in each arm). eTable 1 in Supplement 2 summarizes adverse events that occurred during combination therapy at grade 2 or above in greater than 10% of patients in either arm or that were different significantly between the arms. Grade 3 to 4 adverse events were reported in 41.2% (wP+V) vs 36.7% (wP+P). The most frequent grade 3 to 4 toxic effects were lymphopenia (13% wP+V vs 9% wP+P) and fatigue (9% vs 4%). There was significantly more gastroesophageal reflux (grade 1/2: 10% v 0%), rash (grade 2/3: 9% vs 0%), and lymphopenia (grade 2/3/4:

Figure 1. CONSORT Diagram



ITT indicates intention to treat.

Table. Baseline Characteristics

Characteristic	No. (%)		
	wP+V (n = 70)	wP+P (n = 70)	Total (n = 140)
RECIST measurable disease			
Yes	62 (88.6)	61 (87.1)	123 (87.9)
No	8 (11.4)	9 (12.9)	17 (12.1)
Platinum status			
Refractory (progressed on platinum)	12 (17.1)	13 (18.6)	25 (17.9)
Resistant (progressed within 6 mo of completing platinum)	58 (82.9)	57 (81.4)	115 (82.1)
Lines of previous treatment			
1	9 (12.9)	4 (5.7)	13 (9.3)
2	25 (35.7)	27 (38.6)	52 (37.1)
3	21 (30.0)	22 (31.4)	43 (30.7)
>3	15 (21.4)	17 (24.3)	32 (22.9)
Taxane-free interval, mo			
<6	6 (8.6)	4 (5.7)	10 (7.1)
≥6	58 (82.9)	64 (91.4)	122 (87.1)
No prior taxane	6 (8.6)	2 (2.9)	8 (5.7)
Age, median (IQR), y	65.0 (58-70)	61.0 (58-67)	63.0 (58-69)

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; wP+P, weekly paclitaxel plus placebo; wP+V, weekly paclitaxel plus vistusertib.

47% vs 31%) with wP+V compared with wP+P. There were no grade 4 or 5 events.

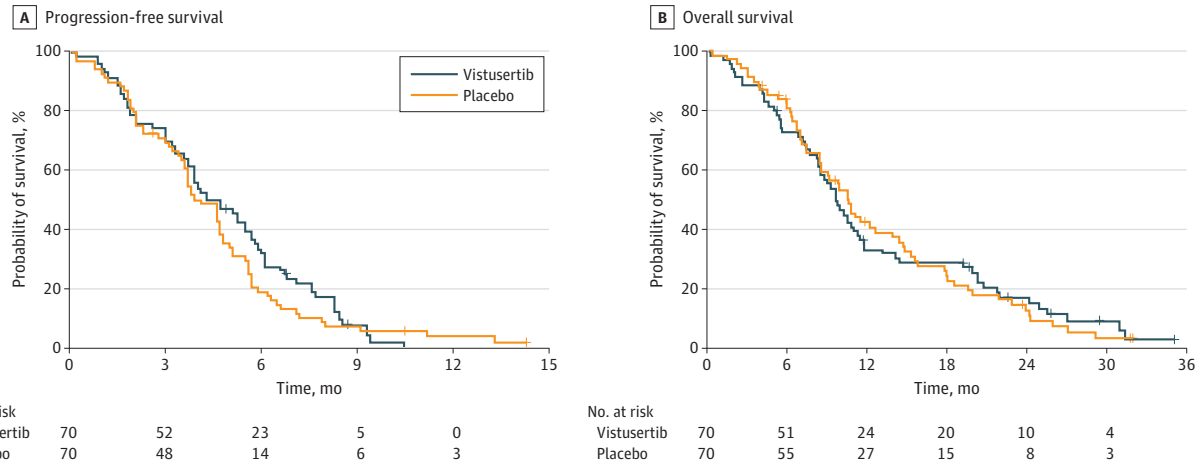
Dose intensity of weekly paclitaxel was similar between the wP+V and wP+P arms (eTable 2 in Supplement 2). Dose reductions, missed doses (eTable 2 in Supplement 2), and dose discontinuation due to toxicity (5% vs 0%) were greater for vistusertib than placebo.

A total of 126 patients were included in the QOL analysis. Overall QOL completion at time points used in the analysis (up to and including week 28) was 79.3%. There were no statistically significant differences (at either 10% or 20% level) between the 2 treatment arms for EQ-5D index or EQ-5D visual analog scale (see eFigure 2 in Supplement 2).

Biomarker Analysis

Digital quantification of IHC PTEN status showed a high correlation between QuPath and pathologist scores (r = 0.94, P < .001 for tumor; r = 0.70, P = .009 for nontumor; eFigure 3 and eFigure 4 in Supplement 2). Expression of PTEN was more variable in tumor (H-score range, 23-258) than nontumor cells (range, 44-177). Using previously described criteria, 13 (19.1%) cases were defined as PTEN low and 55 (80.9%) as PTEN high. There was a significant interaction between the randomization arm and PTEN status (P = .02) for PFS (supporting data in **Figure 3**A). Patients with PTEN-low tumors showed a longer PFS compared with patients with PTEN-high tumors in the experimental arm (median, 9.4 [95% CI, 2.8-16.0] months

Figure 2. Progression-Free Survival and Overall Survival for the Whole Patient Population



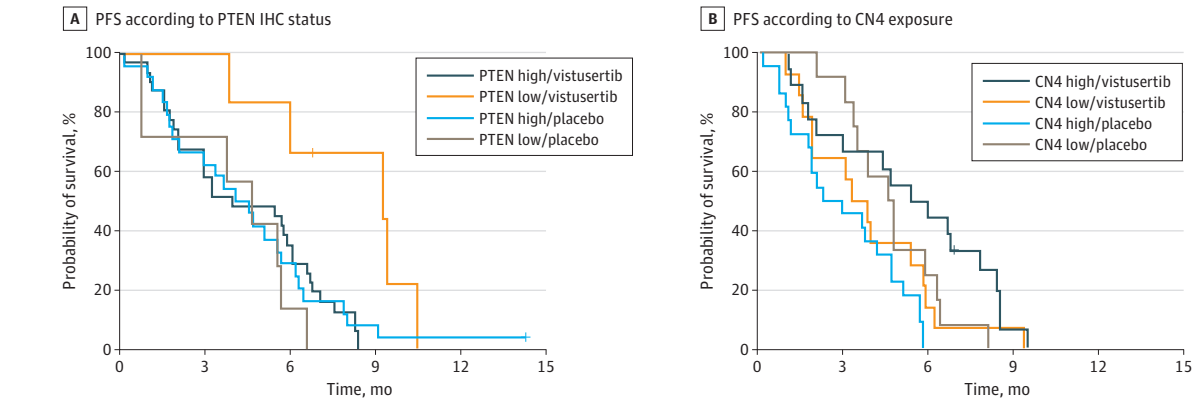
No. at risk

Vistusertib	70	52	23	5	0
Placebo	70	48	14	6	3

No. at risk

Vistusertib	70	51	24	20	10	4
Placebo	70	55	27	15	8	3

Figure 3. Progression-Free Survival According to PTEN IHC Status and CN4 Exposure



No. at risk

PTEN high/vistusertib	31	21	12	0	0
PTEN low/vistusertib	6	6	5	4	0
PTEN high/placebo	24	16	8	3	1
PTEN low/placebo	7	7	2	0	0

No. at risk

CN4 high/vistusertib	18	13	9	3
CN4 low/vistusertib	14	11	3	2
CN4 high/placebo	22	11	0	0
CN4 low/placebo	12	12	4	0

A, Control arm (paclitaxel plus placebo); median progression-free survival (PFS), 4.2 months (PTEN high) vs 4.8 months (PTEN low); experimental arm (paclitaxel plus vistusertib): median PFS 4.1 months (PTEN high) vs 9.4 months (PTEN low). B, Control arm (paclitaxel plus placebo); median PFS, 2.3 months (CN4 high) vs 4.6 months (CN4 low); experimental arm (paclitaxel plus vistusertib): median PFS, 5.4 months (CN4 high) vs 3.3 months (PTEN low). CN4 indicates copy number 4; IHC, immunohistochemistry; PTEN, phosphatase and tensin homolog.

vs 4.1 [95% CI, 1.1-7.0] months, respectively) but not in the control arm (4.8 [95% CI, 2.5-7.0] months vs 4.2 [95% CI, 2.5-5.9] months, respectively) (Figure 3A). No difference in OS was recorded, although there was a trend toward a longer OS for patients with PTEN-low tumors in the experimental arm.

We used shallow whole genome sequencing to analyze genome-wide absolute CN in 78 samples from 66 patients (with 12 matched diagnosis/study-entry pairs). There were no differences in ploidy, rates of focal somatic CN alterations, or CN signature exposure[15] between diagnosis and study-entry (eFigure 5 in Supplement 2), allowing us to combine diagnosis and study-entry samples as a single cohort for survival analyses. No CN signature had a statistically significant predictive value although a trend toward an interaction between the treatment and exposure to normalized signature 4 was recorded for PFS. Therefore, we divided our cohort in 2 groups according to a predefined cutoff, the mean normalized signature 4 exposure. Forty (60.6%) patients had high exposure (defined as greater than or equal to the mean) and 26 (39.4%) low (defined as less than the mean). High exposure to normalized signature 4 was associated with a worse outcome in the control arm with a PFS of 2.3 (95% CI, 0.2-4.4) vs 4.6 (95% CI, 3.1-6.2) months, respectively, but a numerically longer PFS in the experimental arm (Figure 3B). No difference in OS was observed.

Discussion

To our knowledge, OCTOPUS is the first randomized trial to evaluate whether adding a dual mTORC inhibitor to weekly pa-

clitaxel might improve PFS and OS in PR-HGSC. It is also the first platinum-resistant/refractory study exclusively in the HGSC histological subtype and to permit prior weekly paclitaxel treatment. Although the safety profile was manageable, the study failed to reach its primary end point. The observed outcomes in the control arm (overall response rate, 30%; median PFS, 4.4 months; median OS, 11.1 months) were in keeping with previous studies of weekly paclitaxel in this patient population[1] and there was a small improvement in PFS (HR, 0.84) in the experimental arm not accompanied by improved response rate or OS.

Recurrent ovarian cancer that is resistant or refractory to platinum-based chemotherapy has a dismal prognosis, and there have been strikingly few positive randomized clinical trials in this patient population.[16,17] Treatment still relies on single-agent chemotherapy,[18] and previous attempts to improve activity of weekly paclitaxel with targeted drugs have been largely negative in trials that have recruited all histological subtypes of ovarian cancer.[1,19-22] The key exception is bevacizumab.[18] However, the activity of the weekly paclitaxel/bevacizumab combination was reported in an exploratory, subgroup analysis, and use is restricted to patients who are bevacizumab-naive and have received no more than 2 prior lines of therapy.[23-27] This study is the first arm of OCTOPUS, a novel phase 2 umbrella framework that aims to test the addition of new target drugs to weekly paclitaxel, comparing these combinations to a rolling control arm with paclitaxel alone. OCTOPUS provides a flexible and rapid platform to move promising combinations from phase 1 into a randomized assessment with this first arm emphasizing the importance of randomization and embedding biomarker research within clinical trials with a prospective collection of archival and study-entry samples.

Abnormalities in the PI3K/AKT pathway are frequent in HGSC, most commonly due to amplifications or activating mutations in *PIK3CA*, loss of *PTEN* through deletion or genomic rearrangements, and amplification of *AKT1/2*,[28,29] and may be key drivers of drug resistance.[30] However, translating this knowledge into effective therapies has proven extremely challenging,[31] and predictive biomarkers of response in HGSC and other cancers remain elusive.[32] Assessment of single-nucleotide variants in individual genes in the pathway is not predictive,[8] and new data have added complexity, focusing on the importance of PI3K/AKT/mTORC pathway signaling in the tumor microenvironment, including the differentiation and activity of both innate and adaptive immune cell populations.[33,34] Thus, newer biomarkers will need to assess both tumor and nontumor cells and provide readouts of overall pathway activity.

We used 2 potential predictive biomarkers. Digital image analysis allows automated segmentation of tumor vs nontumor cells and produces reproducible and quantitative assessment of protein expression. Given the key role of PTEN in regulating PI3K/AKT/mTORC signaling and the frequency PTEN loss in HGSC,[14] we assessed PTEN expression by IHC using validated protocols.

Using a predefined classification, our results indicate that low tumor cell PTEN expression is associated with improved PFS in the experimental arm but, importantly, not in the control arm. There are conflicting data on the prognostic importance of PTEN loss,[14,35] and our analysis of archival material appears to confirm that PTEN loss is not simply a prognostic biomarker.[14] This is one of the first uses of digital pathological quantification in ovarian cancer trials, but any predictive effect of PTEN loss will need prospective confirmation in a separate study cohort, such as the ongoing DICE trial (weekly paclitaxel with or without TAK-228; NCT03648489).[36]

High-grade serous carcinoma is the archetypal C class tumor,[37] marked by extensive CN abnormalities. However, using genome-wide CN information to inform precision medicine strategies is technically challenging. We recently described CN signatures, patterns of CN alterations in HGSC that reflect underlying mutational processes.[15] Copy number signature 4, marked by high segment CN, was significantly associated with whole genome duplication and mutations in the PI3K/AKT pathway.[15] There is a link between CN signature 4 and high ploidy as well as poor prognosis both in early- and late-stage HGSC.[38] We explored the putative predictive value of CN signature 4 exposure in this study, showing a numerical improvement in PFS in the experimental arm and a worse prognosis in the control arm for patients with high exposure.

Strengths and Limitations

There are several shortcomings in this study. The first and foremost is that it failed to reach its primary end point. Second, by restricting enrollment to patients with HGSC histology only, we excluded cases with endometrioid histology, where PTEN loss is frequent,[39] while our translational biomarker assays, although predefined at the start of the translational studies, were not preplanned and were used neither as stratification factors nor to select patients for study entry. In addition, these analyses are based on a low number of available samples. We used simple cutoffs to define PTEN high vs low and CN signature 4 high vs low, an approach that is applied to other markers such as assays of homologous recombination[40] but is pragmatic rather than biological. Indeed, protein expression and CN signature exposure are continuous variables and application of cutoffs should ideally be based on biological parameters. A further challenge with CN signature analysis is that the data are compositional (ie, sum to 1 in each sample) and interdependent, meaning that any increase in 1 signature must, by definition, be accompanied by a decrease in at least 1 other.

Despite these limitations, the first arm of OCTOPUS has demonstrated that a platform trial design may have utility in PR-HGSC for drug screening, taking into account the low number of patients and the rapid recruitment. However, the non-negligible level of uncertainty inherent in this trial design, in particular the wide type I and II error allowance, means that confirmatory phase 3 trials will always be necessary in the case of positive results. We also showed that it is possible to make study-entry biopsies mandatory in these studies when feasible without compromising recruitment—140 patients were recruited in approximately 24 months, with study-entry biopsies obtained in 64% of participants.

Conclusions

In what is to our knowledge the first randomized clinical trial of a dual mTORC1/2 inhibitor in ovarian cancer, findings showed that the addition of vistusertib to weekly paclitaxel was safe and achievable in PR-HGSC but did not improve PFS or OS in an unselected population. Potential predictive biomarkers will need to be evaluated in separate study cohorts.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Banerjee, Giannone, Ennis, Glasspool, Mirza, Lewsley, Hinsley, McNeish.
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