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Efficacy and safety of olaparib monotherapy in germline *BRCA1/2* mutation carriers with advanced ovarian cancer and three or more lines of prior therapy

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Conflicts of interest

SM Domchek has received research funding from AbbVie, AstraZeneca and Clovis Oncology; C Aghajanian has received honoraria from AstraZeneca, and has received travel allowance and acted in an advisory/consulting role for AbbVie; RK Schmutzler has acted in an advisory/consulting role, and has received honoraria and research funding from AstraZeneca; MW Audeh, M Friedlander, G Fried, SM Stemmer, A Hubert and B Kaufman have received research funding from AstraZeneca; J Balmaña has received honoraria and research funding, and acted in an advisory/consulting role for AstraZeneca; G Mitchell and O Rosengarten have acted in an advisory/consulting role for AstraZeneca and have received research funding from AbbVie and AstraZeneca; JD Robertson and Helen Mann were employees and held stock in AstraZeneca at the time of the study.

R Shapira-Frommer and N Loman declare no conflict of interest.

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Abstract

Objective—The efficacy and safety of olaparib, an oral poly(ADP-ribose) polymerase (PARP) inhibitor, was investigated in a subgroup of patients with germline *BRCA1/2* mutated (g*BRCA1/2*m) advanced ovarian cancer who had received 3 prior lines of chemotherapy. Primary data from this Phase II study (Study 42, ClinicalTrials.gov NCT01078662) have been reported previously.

Methods—Eligible patients were treated with oral olaparib 400 mg bid capsule monotherapy until disease progression according to RECIST v1.1. Objective response rate (ORR) and duration of response (DoR) were assessed for patients with measurable disease at baseline. Safety and tolerability were assessed for all patients by adverse event (AE) incidence and changes in laboratory parameters. Platinum resistance status was obtained retrospectively, and responses to olaparib evaluated.

Results—In patients with g*BRCA1/2*m ovarian cancer, 154/193 (80%) had received 3 prior lines of chemotherapy, of whom 137/154 (89%) had measurable disease at baseline. ORR was 34% (46/137; 95% confidence interval [CI] 26–42) and median DoR was 7.9 (95% CI 5.6–9.6) months. ORR in platinum-resistant tumors was 30%. Median DoR for platinum-sensitive and platinum-resistant disease was similar: 8.2 months (95% CI 5.6–13.5) compared with 8.0 months (4.8–14.8), respectively. Six of the 193 (3%) patients had an AE with an outcome of death. None of these AEs at time of occurrence was considered causally related to olaparib.

Conclusion—Following 3 prior lines of chemotherapy, olaparib 400 mg bid (capsule form) monotherapy demonstrated notable antitumor activity in patients with g*BRCA1/2*m advanced ovarian cancer. No new safety signals were identified.

Keywords

olaparib; ovarian cancer; *BRCA1/2* mutation; Phase II

Introduction

Ovarian cancer, one of the five leading causes of death from cancer in women in the USA, is most frequently diagnosed at an advanced stage [1]. Despite high response rates to initial taxane-platinum-based chemotherapy, the majority of patients will develop persistent or recurrent disease. Recurrences are classified according to platinum-free interval (PFI), which is calculated from the date of the last administered dose of platinum therapy, to the date of progression. Recurrences with a PFI of ≥6 months are considered platinum sensitive and <6 months, platinum resistant. Four Phase III trials have defined the role of platinum doublet therapy for patients with first platinum-sensitive recurrence [2–5].

Patients with recurrent ovarian cancer often receive multiple lines of treatment, with time to progression generally shortening with consecutive therapies; by the third relapse, patients typically have little or no chemotherapy-free interval [6]. There is an urgent need for novel

ovarian cancer treatments that are well tolerated and which will improve outcomes for patients who have received multiple lines of chemotherapy.

Olaparib (Lynparza™) is an oral poly(ADP-ribose) polymerase (PARP) inhibitor with activity in germline *BRCA1/2*-mutated (g*BRCA1/2m*) ovarian cancer [7–9]. Tumors with *BRCA1/2* mutations are characterized by a homologous recombination repair deficiency in DNA repair and appear to be susceptible to PARP inhibitor therapy due to synthetic lethality. In a Phase II study (Study 42 [D0810C00042], ClinicalTrials.gov: NCT01078662), olaparib 400 mg bid monotherapy was evaluated in 298 patients with g*BRCA1/2m* cancers, of whom 193 had recurrent ovarian cancer (mean number of prior chemotherapy regimens 4.3) [8]. All patients were considered platinum resistant, but a subset was platinum sensitive and not considered suitable for further platinum therapy, typically due to hypersensitivity reactions. With olaparib monotherapy, objective tumor response rates in Study 42 were 26% for all patients with g*BRCA1/2m* cancers, and 31% for patients with g*BRCA1/2m* ovarian cancer. Most toxicities were low grade or managed by brief dose interruption or dose reduction [8].

Reported here are data from a heavily pretreated subgroup of patients in this study who had g*BRCA1/2m* ovarian cancer and had received 3 prior lines of chemotherapy. Retrospective data on platinum response status are also reported.

Methods

Study design and patients

The study design, patient population and statistical analyses for this prospective, multicenter, non-randomized Phase II study in patients with g*BRCA1/2m* and advanced recurrent cancers have been described previously in detail [8]. In brief, patients with ovarian cancer were required to have documented progressive or recurrent disease according to either Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or Gynecologic Cancer Intergroup CA 125 criteria, either during or within 6 months of completion of their most recent platinum-based chemotherapy regimen. Patients could also be platinum sensitive but considered not suitable for further platinum therapy. Patients were treated continuously with oral olaparib 400 mg bid (capsule formulation) monotherapy until disease progression or other olaparib discontinuation criteria were met. In the event of toxicity, dose reductions (to 200 or 100 mg bid) and interruptions were permitted. Safety and tolerability were assessed by adverse events (AEs) and changes in laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (version 3). The institutional review board or independent ethics committee of all investigational sites approved the protocol, and the study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca Policy on Bioethics[10].

Further to efficacy data documented previously [8], we report the objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) rate in a subgroup of patients with recurrent ovarian cancer (comprises tumor sites: ovary, fallopian tube and peritoneal) and measurable disease at baseline who had received 3 prior lines of chemotherapy. Efficacy data are stratified according to patients' platinum sensitivity status, which was obtained retrospectively from the study sites following the initial study analysis

in those cases in whom the therapy immediately prior to randomization was not platinum (for these, the data were collected prospectively). Platinum status was defined as (a) sensitive – when time from last platinum was >6 months, (b) resistant – when time from last platinum was <6 months, and (c) refractory – when time from last platinum was <2 months and best response to platinum was progressive disease. Safety and tolerability data are reported for all patients with ovarian cancer, stratified according to prior number of lines of chemotherapy.

Statistical analysis

No formal sample size calculation was performed since the study was exploratory in nature. The first patient was enrolled on February 21, 2010 and last patient last visit was on July 31, 2012. Statistical analyses were performed by the sponsor with SAS (version 8.2).

Patients with a best RECIST score of either complete response (CR), or partial response (PR) had to have a confirmed response at least 28 days later. A CR or PR not maintained for at least 28 days was considered unconfirmed. ORR and DoR were calculated from patients with measurable disease at baseline. ORR was defined as the percentage of patients with at least one visit response of CR or PR that was confirmed at least 4 weeks later (as defined by RECIST v1.1). ORR was summarized and 95% confidence intervals (CIs) for binomial proportions were calculated using the Clopper – Pearson (exact) method. DoR was defined as the time from the date of first documented response (CR/PR) to the date of documented progression (as defined by RECIST v1.1) or death (by any cause) in the absence of disease progression. Median DoR was calculated from the onset of response using the Kaplan-Meier technique. Median time to onset was defined as the time from randomization to the first documented response. The median is the standard 50th percentile for all responding patients. AEs and laboratory parameters were summarized with descriptive statistics.

Results

Patients

In total, 193/298 patients (65% of the overall study population) had ovarian cancer (ovary, n=178; peritoneal, n=11; fallopian tube, n=4). Of the 193 patients, 167 (87%) had measurable disease at baseline, with the majority, 137 (71%) (ovary, n=125; peritoneal, n=9; fallopian tube, n=3), having received three or more prior lines of chemotherapy. Patient demographics and baseline disease characteristics are summarized in Table 1. At data cut-off, 25/193 (13%) patients were still receiving olaparib and 168 (87%) had discontinued, primarily as a result of progressive disease (n=93, 48%), subjective disease progression (n=49, 25%) and withdrawal of consent (n=11, 6%).

Efficacy

For patients with measurable disease who received 3 prior lines of chemotherapy (n=137), there were 46 confirmed responders (Table 2). The ORR was 34%; CR was observed in 2/137 (2%) patients and PR in 44/137 (32%). An additional 31/137 (23%) patients had stable disease (for a minimum of 16 weeks following start of treatment). Platinum resistant/sensitive status was available for 134/137 (98%) patients. The ORR was highest at 46% in

patients considered platinum sensitive (but not considered suitable to receive further platinum therapy); for patients designated platinum resistant, it was 30%, and for those designated platinum refractory, it was 14%. Stable disease was seen in 26% and 24% in those with platinum-sensitive and platinum-resistant disease, respectively, compared to 14% in those with platinum-refractory disease. ORRs with olaparib were 50–57% for platinum-sensitive patients and 31–39% for platinum-resistant patients who had received three, four or five prior lines of therapy; they were lower for those who had received 6 prior lines of therapy (20% for platinum-sensitive and 13% for platinum-resistant patients) (Fig. 1). The median DoR was 7.9 months, and DoR was similar for both platinum-sensitive and platinum-resistant patients (8.2 and 8.0 months, respectively).

PFS was analyzed for the 154 evaluable ovarian cancer patients with >3 prior regimens. Median PFS was 6.7 months (95% CI 5.5–7.6). Median PFS was 9.4 months (95% CI 6.7–11.4) and 5.5 months (4.2–6.7) in the platinum-sensitive versus platinum-resistant subgroups, respectively.

Treatment duration

For patients with advanced *gBRCA1/2m* ovarian cancer and measurable disease at baseline who had received 3 prior chemotherapy regimens (n=137), at data cut-off median total treatment duration was 168 days (range 1–819) and median actual treatment duration (ie excluding dose interruptions) was 158 days (range 1–780). At the time of writing, 13 of the 137 patients have remained on olaparib treatment for >2 years (six patients were platinum sensitive, five platinum resistant and two of unknown platinum sensitivity). Of these 13, four have remained on treatment for >3–4 years (two platinum sensitive, two platinum resistant) and two for >4 years (one platinum sensitive, one platinum resistant).

Safety

The mean daily dose of olaparib in the total treated ovarian cancer population (n=193) for actual treatment duration was 741.1 mg (mean range 321.4–800.0) and mean dose adherence was 93% (range 40–100). Dose interruptions were reported in 83 (43%) patients, most frequently as a single interruption (42 patients, 22%). A dose reduction was also implemented in 42 (22%) patients.

One hundred of 193 patients (52%) experienced an AE of grade 3; of these, 57/193 (30%) incidences were considered causally related to olaparib, by an investigator. Six out of 193 (3%) patients, all of whom had received 3 prior chemotherapy regimens, experienced an AE with an outcome of death (myelodysplasia leading to acute leukemia, acute myeloid leukemia, cerebrovascular accident, chronic obstructive pulmonary disease, pulmonary embolism, wound dehiscence), that at the time of the occurrence was not considered causally related to olaparib. Time from last dose of olaparib to the onset of acute leukemia was 25 days and –151 days; the minus sign (–151 days) indicates that the AE occurred before the patient finished treatment. In this particular case, the investigator advised the patient to discontinue olaparib treatment, but the patient wished to continue. In consideration of the good response in this patient, the investigator decided to proceed with olaparib treatment at a reduced dose of 200 mg bid under regular monitoring of blood counts. Serious

AEs (SAEs) were reported in 58/193 (30%) patients, most frequently anemia (12 patients, 6%), abdominal pain (10, 5%), intestinal obstruction (7, 4%) and pleural effusion (4, 2%). Of the 58 patients (counting patients with multiple SAEs once), 20 (10%) had an SAE considered causally related to olaparib, most frequently anemia (12 patients, 6%), vomiting (3, 2%), neutropenia (2, 1%), thrombocytopenia (2, 1%), and febrile neutropenia, leucopenia, pancreatitis, hemoglobin decrease and dyspnea (all one patient, 0.5%).

The proportions of patients experiencing any AE, or any AE of grade 3, were similar in patients who had received ≥ 3 prior chemotherapy regimens ($n=154$) and in all patients with ovarian cancer ($n=193$) in the study (98% vs 97% and 55% vs 52%, respectively). The most frequently reported AEs for patients with ovarian cancer receiving ≥ 3 prior lines of chemotherapy ($n=154$) are shown in Table 3. Nine out of 193 (5%) patients, all of whom had received ≥ 3 prior chemotherapy regimens, discontinued olaparib treatment as a result of 12 AEs of abdominal pain ($n=3$), anemia, cerebrovascular accident, gastroesophageal reflux, nausea, increased hepatic enzymes, intestinal obstruction, leukopenia, thrombocytopenia and vomiting (all $n=1$). Important abnormalities in clinical chemistry values during olaparib treatment (maximum CTCAE grade achieved) included Grade 3 changes in alanine aminotransferase (3/193 patients, 2%), alkaline phosphatase (five patients, 3%), aspartate aminotransferase (one patient, 1%), gamma glutamyltransferase (16 patients, 9%) and total bilirubin (five patients, 3%). There were no patients with Grade 4 changes, except in gamma glutamyltransferase (4/193 patients, 2%).

Discussion

In the Phase II study (NCT01078662) subgroup analysis reported here, patients with relapsed *gBRCA1/2* ovarian cancer who had received ≥ 3 prior lines of chemotherapy and with measurable disease ($n=137$) experienced clinical benefit (assessed by ORR and DoR) from olaparib 400 mg bid monotherapy.

The ORR and DoR values reported here (ORR 34% [95% CI 26–42], DoR 7.9 months [95% CI 5.6–9.6]) are similar to the overall response rate for all ovarian cancer patients with measurable disease in the Phase II study (ORR 36% [95% CI 29–44], DoR 7.4 months [95% CI 5.5–9.2]) (ie, patients with either platinum-resistant disease or unable to receive further platinum therapy who had received ≥ 1 prior line of chemotherapy). Previous reports, including a pooled analysis of 1620 ovarian cancer patients from three randomized Phase III trials of cytotoxic systemic chemotherapy, suggest diminishing returns with limited benefits after more than three lines of systemic therapy in patients with recurrent ovarian cancer [6]. However, the results we report suggest that olaparib monotherapy has relatively high activity, even after multiple lines of chemotherapy, and is associated with objective responses in almost 40% of patients with clinically meaningful duration of response, and tolerable toxicity. At the time of writing, seven patients have remained on treatment for 2–3 years, four for 3–4 years and two for more than 4 years (all had received ≥ 3 prior lines of chemotherapy).

The majority of the patients receiving ≥ 3 prior lines of chemotherapy and with measurable disease in the subanalysis reported here had disease considered platinum resistant (59%) or

refractory (10%), compared with 28% with disease that was platinum sensitive but unsuitable for further platinum-based therapy. Although details are not available for all patients, hypersensitivity reactions, excessive nausea and vomiting, and accumulating toxicity appeared to be the main reasons patients were considered unsuitable for additional platinum therapy. In prior studies [11], platinum-sensitive tumors were associated with the greatest clinical benefit from olaparib, and the ORR reported here was indeed highest (46%) for patients with platinum-sensitive tumors. Of note, in platinum-resistant tumors, the ORR was 30%, which was notably higher than might be anticipated. Importantly, the median DoR for platinum-sensitive versus platinum-resistant disease was similar: 8.2 months (95% CI 5.6–13.5) compared with 8.0 months (4.8–14.8), respectively. Finally, although the number of patients was very small, some responses were seen in platinum-refractory diseases (2/14, 14%). These findings are consistent with prior studies that found a clear association with response to olaparib and platinum sensitivity/resistance [12]. For example, in Fong *et al.*, response (defined as RECIST response or CA125 responses) was highest in women with platinum-sensitive tumors (6/13, 46%), followed by platinum-resistant tumors (8/24, 33%) and platinum-refractory tumors (0/13, 0%) [12].

With the exception of abdominal pain, which may be associated more with the disease under study, the most commonly reported AEs (low-grade nausea, fatigue, vomiting, and anemia) are consistent with the known toxicity profile of olaparib [13–15]. No new safety findings were identified in this heavily pretreated patient population, and discontinuation of therapy because of an AE was rare. The safety profile in patients receiving 3 prior lines of chemotherapy was similar to that of the overall population. Similar toxicity profiles to that of olaparib have been documented in clinical trials with other PARP inhibitors [16].

The results reported here indicate that heavily pretreated patients with g*BRCA1/2*m ovarian cancer, who have received 3 prior lines of chemotherapy, receive meaningful clinical benefit from olaparib even in the late-line treatment setting. A Phase III trial in patients with platinum-sensitive relapsed serous ovarian cancer who have a *BRCA1/2* mutation and have previously received 2 lines of platinum-based chemotherapy is currently ongoing (SOLO3, NCT02282020).

Conclusion

Olaparib 400 mg bid (capsule form) monotherapy in patients with g*BRCA1/2*m advanced ovarian cancer who had received 3 prior lines of chemotherapy demonstrated notable antitumor activity, including platinum-resistant patients. The safety profile of olaparib in this heavily pretreated population was consistent with that observed in previously reported olaparib monotherapy studies.

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Highlights

- Patients with germline *BRCA1/2* mutated (g*BRCA1/2*m) ovarian cancer and 3 prior lines of chemotherapy experienced clinical benefit from olaparib
- Objective response rate was higher for patients with platinum-sensitive versus platinum-resistant tumors; however, median duration of response was similar
- No new safety findings were identified in this heavily pretreated population

Fig. 1.

Objective response rate by platinum sensitivity status* stratified by number of prior lines of chemotherapy in patients with g*BRCA1/2*m ovarian cancer who received 3 lines of prior chemotherapy.

Table 1Demographics and baseline disease characteristics for patients with measurable^a disease at baseline

Parameter	Patients with ovarian cancer (n=167)	Patients with ovarian cancer receiving 3 prior lines of chemotherapy (n=137)
Median age (range), years	57 (29–79)	58 (35–79)
Age group, years, n (%)		
<50	34 (20.4)	26 (19.0)
50 to <65	99 (59.3)	83 (60.6)
65	34 (20.4)	28 (20.4)
Race, n (%)		
White	158 (94.6)	129 (94.2)
Black/African American	1 (0.6)	1 (0.7)
Asian	7 (4.2)	6 (4.4)
Other	1 (0.6)	1 (0.7)
ECOG performance status, n (%)		
0	96 (57.5)	76 (55.5)
1	62 (37.1)	52 (38.0)
2	8 (4.8)	8 (5.8)
Unknown	1 (0.6)	1 (0.7)
<i>gBRCA</i> mutation status, n (%)		
<i>BRCA1</i>	126 (75.4)	106 (77.4)
<i>BRCA2</i>	40 (24.0)	30 (21.9)
Both	1 (0.6)	1 (0.7)
Prior chemotherapy regimens, n (%)		
1	7 (4.2)	N/A
2	23 (13.8)	N/A
3	41 (24.6)	41 (29.9)
4	26 (15.6)	26 (19.0)
5	24 (14.4)	24 (17.5)
6–14	46 (27.5)	46 (33.6)

^aDefined by response evaluation criteria in solid tumors v1.1

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N/A, not applicable

Table 2

Objective response rate and duration of response stratified by platinum sensitivity status in patients with g*BRCA1/2*m ovarian cancer and measurable disease at baseline who had received 3 prior chemotherapy regimens (n=137).

Platinum sensitivity status ^a (N=total patients with measurable disease)	Confirmed responders ^b n	ORR, % (95% CI)	Median DoR, months (95% CI)
Total (N=137)	46	34 (26–42)	7.9 (5.6–9.6)
Platinum sensitive (N=39) ^c	18	46 (30–63)	8.2 (5.6–13.5)
Platinum resistant (N=81)	24	30 (20–41)	8.0 (4.8–14.8)
Platinum refractory (N=14)	2	14 (2–43)	6.4 (5.4–7.4)
Platinum status unknown (N=3)	2	67 (9–99)	6.3 (4.7–7.9)

^aSensitive, time from completion of last platinum therapy to study start (TFP) >6 months; resistant, TFP <6 months; refractory, TFP <2 months and best response to last platinum was progressive disease

^bConfirmed CR or PR

^cPlatinum sensitive but ineligible to receive further platinum-based chemotherapy

Abbreviations: CI, confidence interval; DoR, duration of response; NC, not calculated; ORR, objective response rate

Table 3

AEs (any grade) in >15% or grade 3 AEs in >5% of patients with ovarian cancer in the study receiving 3 prior lines of chemotherapy (n=154)

Patients with ovarian cancer receiving 3 prior lines of chemotherapy (n=154)		
Adverse event by preferred term	All grades n (%)	Grade 3 n (%)
Any adverse event	151 (98)	84 (55)
Nausea	93 (60)	1 (1)
Fatigue	85 (55)	10 (7)
Vomiting	68 (44)	4 (3)
Anemia	53 (34)	31 (20)
Abdominal pain	44 (29)	13 (8)
Diarrhea	46 (30)	2 (1)
Dysgeusia	29 (19)	0
Dyspepsia	33 (21)	0
Decreased appetite	31 (20)	1 (1)
Headache	22 (14)	0
Constipation	22 (14)	2 (1)
Cough	23 (15)	0
Dyspnea	23 (15)	6 (4)