OLAPARIB MAINTENANCE MONOTHERAPY FOR PATIENTS WITH NON-GERMLINE BRCA1/2-MUTATED PLATINUM-SENSITIVE RELAPSED OVARIAN CANCER: PHASE IIIB OPINION INTERIM ANALYSIS

Andrés Poveda,[1] Stephanie Lheureux,[2] Nicoletta Colombo,[3] David Cibula,[4] Kristina Lindemann,[5] Johanne Weberpals,[6] Maria Bjurberg,[7] Ana Oaknin,[8] Magdalena Sikorska,[9] Antonio González-Martín,[10] Radoslaw Madry,[11] María Rubio Pérez,[12] Richard Davidson,[13] Christopher Blakeley,[13] James Bennett,[13] Alan Barnicle,[13] Erik Škof[14]

[1]Initia Oncology, Valencia, Spain; [2]Princess Margaret Hospital, Toronto, Canada; [3]University of Milan-Bicocca and European Institute of Oncology IRCCS, Milan, Italy; [4]General University Hospital in Prague, First Faculty of Medicine, Charles University, Prague, Czech Republic; [5]Oslo University Hospital, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [6]Ottawa Hospital Cancer Center, Ottawa, Canada; [7]Skåne University Hospital, Lund University, Lund, Sweden; [8]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [9]Olsztyn Provincial Specialist Hospital, Olsztyn, Poland; [10]Clinica Universidad de Navarra, Madrid, Spain; [11]Clinical Hospital of the Transfiguration of the Lord's Medical University Karol Marcinkowski, Poznań, Poland; [12]Hospital Universitario Reina Sofía, Córdoba, Spain; [13]AstraZeneca, Cambridge, UK; [14]Institute of Oncology Ljubljana, Ljubljana, Slovenia

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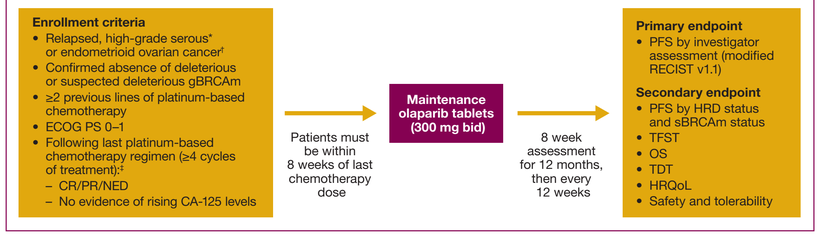
Introduction and Methods

- Maintenance olaparib significantly improved progression-free survival (PFS), versus placebo, in both the Phase II Study 19 trial[1] (NCT00753545) in patients with platinum-sensitive relapsed ovarian cancer (PSR OC) with or without a *BRCA* mutation (BRCAm), and the Phase III SOLO2 trial[2] (NCT01874353) in patients with PSR OC and a BRCAm.
- In Study 19, a significant prolongation of PFS with maintenance olaparib (capsules), versus placebo, was observed in patients with or without a BRCAm
  - In the subgroup of patients without a BRCAm (n=118), a median PFS of 7.4 months was observed with olaparib (versus 5.5 months with placebo; hazard ratio 0.54 [95% confidence interval (CI) 0.34–0.85]),[3] as well as clinically meaningful long-term benefit, with 12% of patients (7/57) receiving olaparib maintenance monotherapy for 6 years or longer.[4]
- We present a planned interim analysis of the Phase IIIb, single-arm, international OPINION study (NCT03402841) investigating olaparib (tablet formulation) maintenance monotherapy in non-germline BRCAm (gBRCAm) PSR OC patients who had received ≥2 previous lines of platinum-based chemotherapy.[5]
- Detailed study methods can be found in the Supplementary Material (accessed via QR code).

Figure 1. Study design



*Including primary peritoneal and/or fallopian tube cancer; †Histologically diagnosed; ‡Use of bevacizumab was not permitted.
bid, twice daily; CA, cancer antigen; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; NED, no evidence of disease; OS, overall survival; PS, performance status; PR, partial response; sBRCAm, somatic BRCA mutation; TDT, time to treatment discontinuation or death; TFST, time to first subsequent therapy or death.

Results

Table 1. Patient characteristics at baseline

	Olaparib (N=279)
Age, years	
Mean (SD)	64.0 (9.19)
Range	40–85
Absence of gBRCAm at screening	
Yes	263 (94.3)
No	0
Unknown	16 (5.7)
Primary tumor location	
Ovary	219 (78.5)
Fallopian tube	41 (14.7)
Primary peritoneal	19 (6.8)
Histology type	
Serous	259 (92.8)
Endometrioid	12 (4.3)
Other	8 (2.9)
Number of prior platinum-chemotherapy regimens	
0 or 1*	4 (1.4)
2	168 (60.2)
>2	107 (38.4)
Objective response to latest platinum-chemotherapy	
CR/NED	93 (33.3)
PR	180 (64.5)
Stable disease*	2 (0.7)
Other*,†	4 (1.4)
ECOG performance status	
0	190 (68.1)
1	89 (31.9)

n (%) presented unless otherwise stated.
*Protocol violators; †Not applicable or missing.
SD, standard deviation.

Patient disposition, characteristics and follow-up

- 371 patients were screened, and 279 patients were enrolled in the study from 17 countries (from February 2018 to April 2019).
- At the time of the interim analysis data cut-off (November 15, 2019), 124 patients (44.4%) were still receiving olaparib and 15 patients (5.4%) had died.
- Median treatment duration with olaparib was 8.2 months (range 0–21.3 months).
- Patient characteristics at baseline are summarized in Table 1 and patient HRD and sBRCAm status following Myriad testing is shown in Table 2.

Table 2. Myriad biomarker analyses: tBRCA and sBRCA mutation status and HRD status

	Olaparib (N=279)
tBRCAm	37 (13.3)
sBRCAm	34 (12.2)
gBRCAm	0
sBRCAm/gBRCAm status not defined	3 (1.1)
Non-tBRCAm	232 (83.2)
HRD-positive	94 (33.7)
HRD-negative	115 (41.2)
HRD test failed	23 (8.2)
tBRCA test failed, cancelled or missing	10 (3.6)

n (%) presented.
tBRCAm, tumor BRCA mutation.

Efficacy

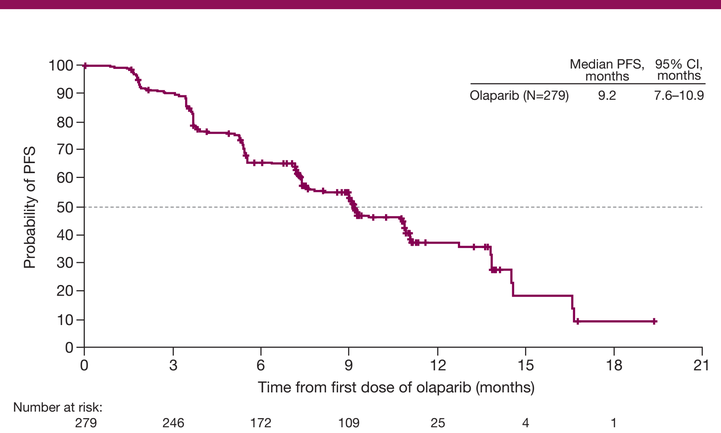
- Median PFS was 9.2 (95% CI 7.6–10.9) months, with 152 PFS events (54.5% maturity) (Figure 2). These were all RECIST progression and there were no deaths in the absence of progression.
  - The percentage of patients who were progression-free at 6 months and 12 months was 65.6% (95% CI 59.6–71.0) and 37.0% (95% CI 29.8–44.3), respectively.
- The median PFS for HRD-positive (excluding sBRCAm) and HRD-negative patients was 9.7 (95% CI 8.1–11.1) and 7.3 (95% CI 5.5–9.1) months, respectively, and 14.5* (9.2 to not evaluable [NE]) months for patients with sBRCAm (Figure 3; Table 3).
- The PFS for patient subgroups based on the number of prior platinum-based chemotherapy regimens (2 vs >2) and objective responses to latest platinum-based chemotherapy (CR or NED vs PR) can be found in Table 3.
- The median TFST was 13.4 (95% CI 11.4–17.7) months (Figure S1).

**This median is unstable because of a lack of events – less than 50% maturity.*

Conclusions

- In this interim analysis of the OPINION study, maintenance olaparib tablets demonstrated relevant activity in patients with non-gBRCAm PSR OC, with a median PFS of 9.2 months
  - The PFS outcome was supported by a median TFST of 13.4 months.
- Activity was seen across all patient subgroups, regardless of HRD and BRCAm status, objective response to latest platinum chemotherapy, or number of prior platinum chemotherapy regimens
  - In HRD-positive patients (excluding sBRCAm), median PFS was 9.7 months.
- The safety profile was consistent with that known for olaparib, with no new safety signals observed
  - Only 15.1% of patients required dose reduction and 7.2% discontinued treatment due to a TEAE.
- Additional follow-up will provide further information on the efficacy of olaparib in patients with non-gBRCAm PSR OC.

Figure 2. Kaplan–Meier plot of PFS



Author contact details: apoveda@initiaoncologia.com.

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Figure 3. Kaplan–Meier plot of PFS by HRD/BRCAm status

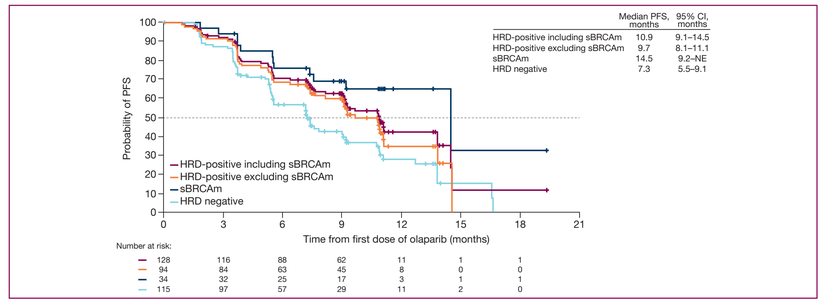


Table 3. PFS outcomes by key subgroups

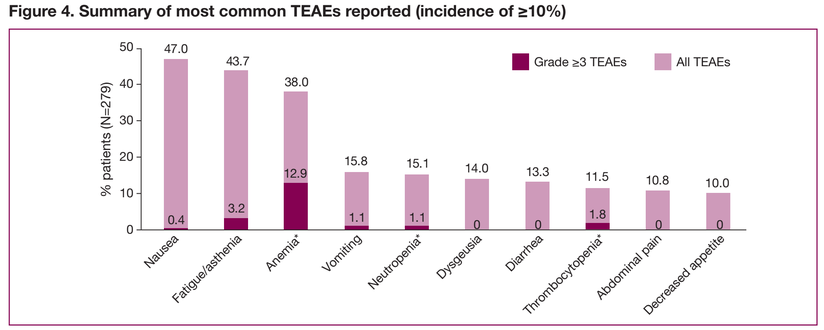
	No. of events/N (%)	Median PFS, months (95% CI)	PFS at 6 months, % (95% CI)	PFS at 12 months, % (95% CI)
HRD/BRCAm status				
HRD-positive including sBRCAm	63/128 (49.2)	10.9 (9.1–14.5)	70.5 (61.7–77.7)	42.2 (31.0–53.1)
HRD-positive excluding sBRCAm	51/94 (54.3)	9.7 (8.1–11.1)	68.6 (58.0–77.0)	34.5 (21.8–47.7)
sBRCAm	12/34 (35.3)	14.5 (9.2–NE)	75.9 (57.5–87.2)	64.9 (45.3–79.1)
HRD-negative	72/115 (62.6)	7.3 (5.5–9.1)	56.7 (46.8–65.5)	27.9 (17.8–38.9)
Number of prior platinum chemotherapy regimens*				
2	96/168 (57.1)	9.2 (7.4–10.9)	66.4 (58.6–73.1)	35.5 (26.2–44.8)
>2	55/107 (51.4)	9.0 (7.2–NE)	64.3 (54.3–72.7)	39.9 (28.7–50.9)
Objective response to latest platinum chemotherapy†				
CR/NED	44/93 (47.3)	10.8 (9.2–13.8)	80.1 (70.3–87.0)	42.9 (29.6–55.4)
PR	104/180 (57.8)	7.6 (7.2–10.9)	58.8 (51.1–65.7)	34.6 (25.8–43.5)

*4 patients were excluded from this analysis; †6 patients were excluded from this analysis.

Safety

- 263 patients (94.3%) experienced at least one treatment-emergent adverse event (TEAE) at data cut-off (Figure 4).
- Most TEAEs were Grade 1 or 2; Grade ≥3 TEAEs occurred in 72 patients (25.8%; Grade 3, 67 patients [24.0%]; Grade 4, 5 patients [1.8%]; no patients had a Grade 5 TEAE)
  - The most common Grade ≥3 TEAEs reported were anemia (12.9%) and fatigue/asthenia (3.2%).
- Serious TEAEs were reported in 52 patients (18.6%), though only two serious TEAEs occurred in >1 patient (anemia [7.9%] and pneumonia [1.1%]).
- There were two cases of new primary malignancies (0.7%; breast cancer and rectal adenocarcinoma), two cases of pneumonitis (0.7%), and one case of myelodysplastic syndrome (0.4%).
- TEAEs led to dose interruption, dose reduction, and treatment discontinuation in 108 (38.7%), 42 (15.1%), and 20 (7.2%) patients, respectively.

Figure 4. Summary of most common TEAEs reported (incidence of ≥10%)



*Grouped-term data.

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