Olaparib maintenance monotherapy for patients with non-germline BRCA1/2-mutated platinum-sensitive relapsed ovarian cancer: Phase IIIb OPINION interim analysis

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Introduction

- Maintenance olaparib significantly improved PFS, vs placebo, in both the Phase II Study 19 trial[1] (NCT00753545) in patients with PSR OC with or without a 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), vs 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 (vs 5.5 months with placebo; HR 0.54 [95% 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-gBRCAm PSR OC patients who had received ≥2 previous lines of platinum-based chemotherapy.[5]

BRCAm, *BRCA* mutation; CI, confidence interval; gBRCAm, germline BRCAm; HR, hazard ratio; PFS, progression-free survival; PSR OC, platinum-sensitive relapsed ovarian cancer.

1. Ledermann J *et al. N Eng J Med* 2012;366:1382–92; 2. Pujade-Lauraine E *et al. Lancet Oncol* 2017;18:1274–84; 3. Ledermann J *et al. Lancet Oncol* 2014;15:852–61;
4. Friedlander M *et al. Br J Cancer* 2018;119:1075–85; 5. Poveda AM *et al. Future Oncol* 2019;15:3651–63.

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Key patient eligibility criteria

- Patients must have had histologically-diagnosed, relapsed, high-grade serous (including primary peritoneal and/or fallopian tube cancer) or endometrioid ovarian cancer, and confirmed absence of deleterious or suspected deleterious gBRCAm.
- Patients must have completed of ≥2 previous lines of platinum-based chemotherapy.
- For the penultimate platinum-based chemotherapy regimen prior to enrollment:
  - Patients must have been platinum sensitive after this treatment; defined as disease progression greater than 6 months after completion of their last dose of platinum chemotherapy.
- For the platinum-based chemotherapy regimen prior to enrollment:
  - Patients must have received at least four cycles of treatment and olaparib must have been initiated within 8 weeks of their last dose of chemotherapy
  - Patients must have been in complete response or partial response, or have no evidence of disease, and have no evidence of rising cancer antigen-125 levels at time of enrollment
  - Use of bevacizumab during this course of treatment was not permitted.

gBRCAm, germline BRCA mutation.

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Study design (1 of 2)

Enrollment criteria

- Relapsed, high-grade serous* or endometrioid ovarian cancer†
- Confirmed absence of deleterious or suspected deleterious gBRCAm
- ≥2 previous lines of platinum-based chemotherapy
- ECOG PS 0–1
- Following last platinum-based chemotherapy regimen (≥4 cycles of treatment):‡
  - CR/PR/NED
  - No evidence of rising CA-125 levels

Patients must be within 8 weeks of last chemotherapy dose

Maintenance olaparib tablets (300 mg bid)

8-week assessment for 12 months, then every 12 weeks

Primary endpoint

- PFS by investigator assessment (modified RECIST v1.1)

Secondary endpoints

- PFS by HRD status and sBRCAm status
- TFST
- OS
- TDT
- HRQoL
- Safety and tolerability

*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; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; sBRCAm, somatic BRCA mutation; TDT, time to treatment discontinuation or death; TFST, time to first subsequent therapy or death.

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Study design (2 of 2)

- Patients received maintenance olaparib tablets (300 mg bid) until investigator-assessed disease progression, unacceptable toxicity, or other protocol-specified criterion for withdrawal
  - Patients could continue to receive olaparib beyond progression if they were deemed by the investigator to be experiencing benefit from treatment and did not meet any other discontinuation criteria.
- Confirmation of non-gBRCAm status via a local test was an enrollment criterion. Additionally, all patients enrolled had a central germline test performed at Myriad using the Myriad myRisk assay to assess non-gBRCAm status. This was available after completion of the interim analysis and is planned to be integrated into the primary analysis of the study.
- For patients discontinued from olaparib, subsequent treatment options were at the discretion of their investigator.

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Endpoints and assessments

- The primary endpoint was investigator-assessed PFS according to modified RECIST v1.1.
- Key secondary efficacy endpoints included investigator-assessed PFS by tumor HRD status (assessed with the Myriad myChoice HRD plus test; HRD-positive: score ≥42) and sBRCAm status, and TFST.

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Statistical analyses

- The OPINION trial was designed to estimate PFS rather than to test a formal hypothesis.
- Simulations were performed assuming 250 patients were enrolled over a 12-month period, with 50% of patients enrolled after 8 months, a median PFS of 8.5 months, and a piecewise exponential model for PFS.
- The primary analysis is planned approximately 30 months after the first patient was enrolled, when it is expected that ~180 PFS events will have been observed (72% maturity).
- This interim analysis was planned to occur after ~135 events (54% maturity) had been observed, anticipated to be 18 months after the first patient was enrolled, and would give a mean 95% CI width of 3.87 months for PFS.
- PFS was summarized using the Kaplan–Meier method, with survival curves depicting the proportion of patients alive and without a PFS event, as well as estimates of median PFS and associated 95% CI. TFST was analyzed using the same methodology.

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Results: 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 DCO (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).

DCO, data cut-off.

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Patient characteristics at baseline

	Olaparib (N=279)
Age, years	
Mean (SD)	64 (9.19)
Range	40–85
Absence of gBRCAm at screening, n (%)	
Yes	263 (94.3)
No	0
Unknown	15 (5.7)
Primary tumor location, n (%)	
Ovary	219 (78.5)
Fallopian tube	41 (14.7)
Primary peritoneal	19 (6.8)
Histology type, n (%)	
Serous	259 (92.8)
Endometrioid	12 (4.3)
Other	8 (2.9)

	Olaparib (N=279)
Number of prior platinum-containing regimens, n (%)	
0 or 1*	4 (1.4)
2	168 (60.2)
>2	107 (38.4)
Objective response to latest platinum-chemotherapy, n (%)	
CR/NED	93 (33.3)
PR	180 (64.5)
Stable disease*	2 (0.7)
Other*,†	4 (1.4)
ECOG performance status, n (%)	
0	190 (68.1)
1	89 (31.9)

*Protocol violators; †Not applicable or missing.
SD, standard deviation.

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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)

tBRCAm, tumor BRCA mutation.

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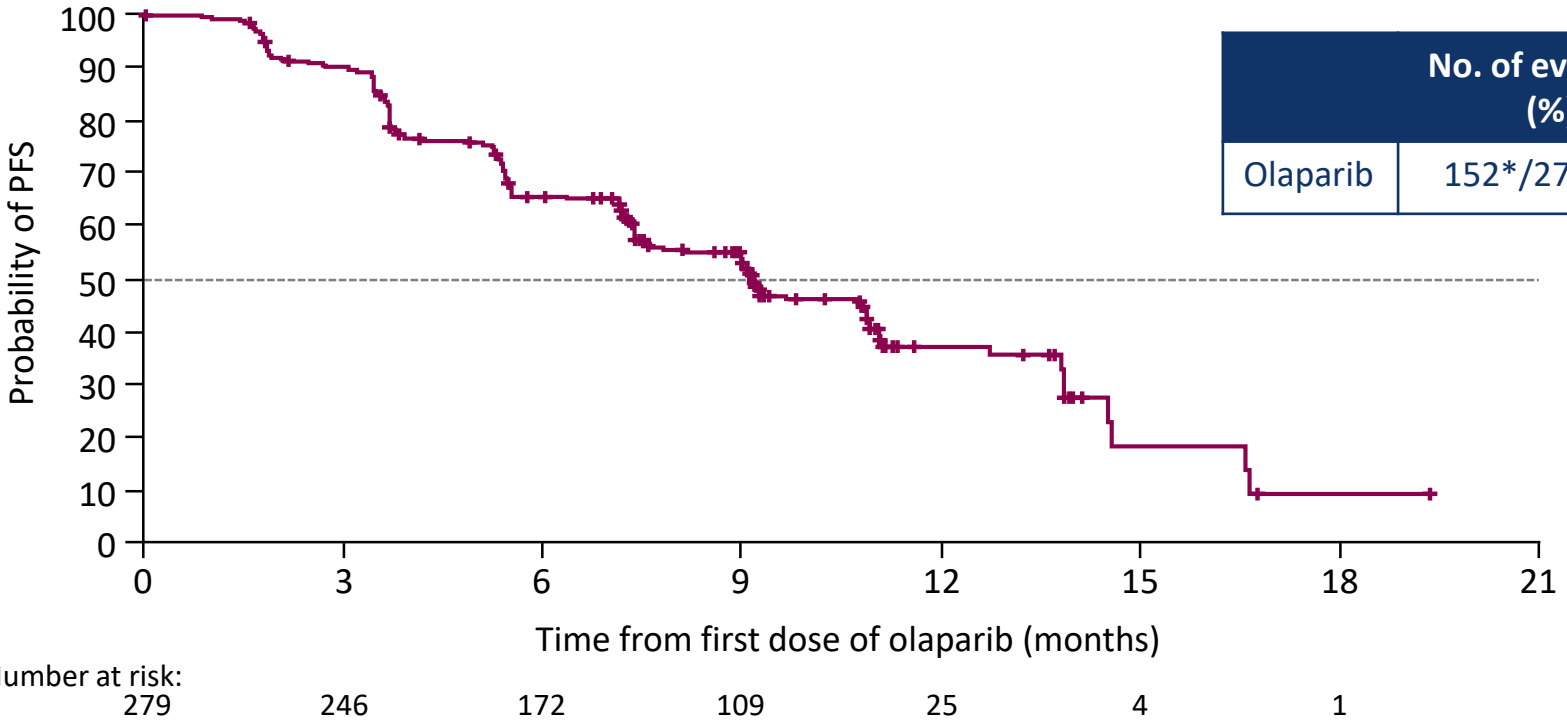
Results: PFS (efficacy analysis set)

- Median PFS was 9.2 (95% CI 7.6–10.9) months, with 152 PFS events (54.5% maturity). 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.



	No. of events/N (%)	Median PFS, months (95% CI)
Olaparib	152*/279 (54)	9.2 (7.6–10.9)

*These were all RECIST progression and there were no deaths in the absence of progression.

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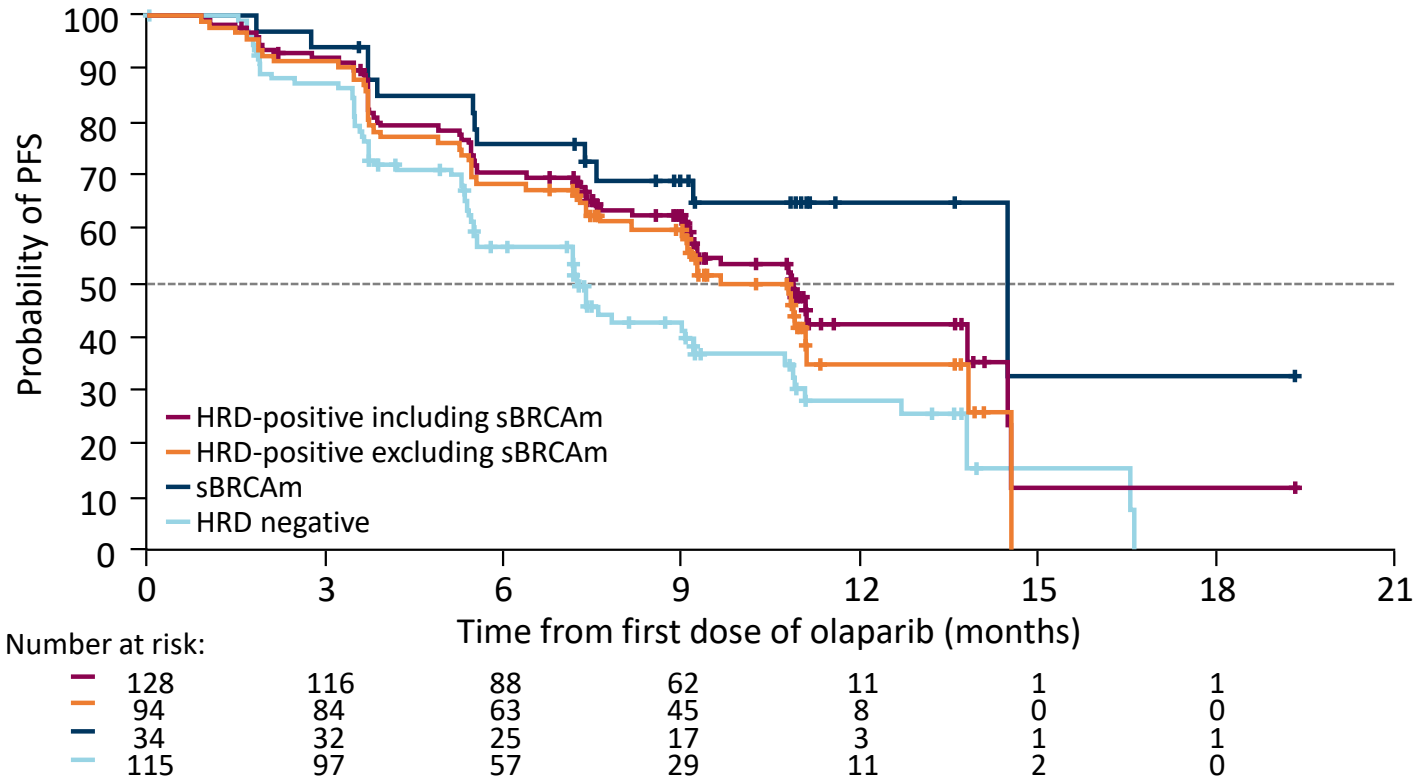
Results: PFS by HRD/BRCAm status

- 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) months for patients with sBRCAm.



	No. of events /N (%)	Median PFS, months (95% CI)	PFS at 6 months, % (95% CI)	PFS at 12 months, % (95% CI)
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)

*This median is unstable because of a lack of events – less than 50% maturity.
NE, not evaluable.

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PFS by prior lines of, and response to, platinum-based chemotherapy

	No. of events/N (%)	Median PFS, months (95% CI)	PFS at 6 months, % (95% CI)	PFS at 12 months, % (95% CI)
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.

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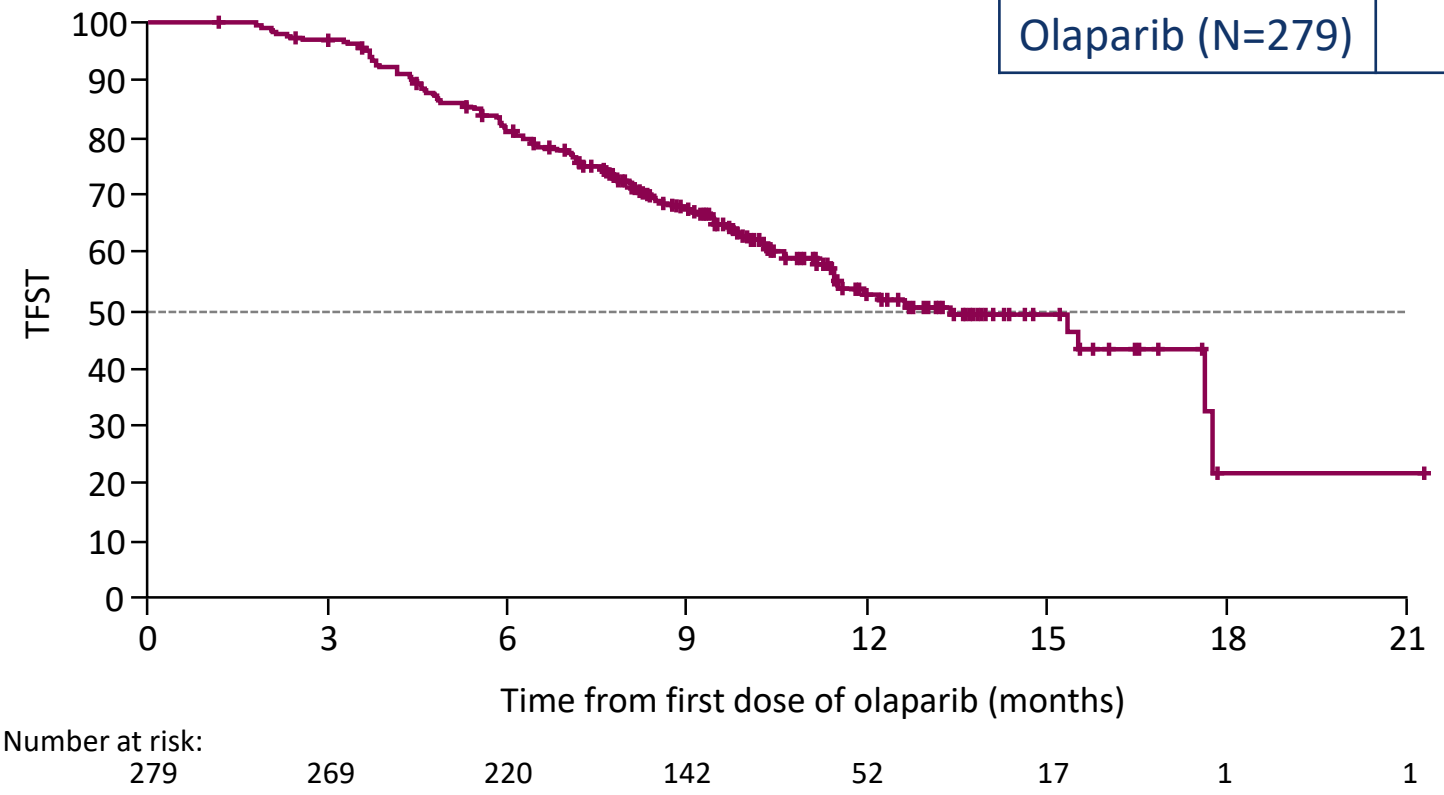
Time to first subsequent therapy of death (efficacy analysis set)

	Median TFST, months	95% CI, months
Olaparib (N=279)	13.4	11.4–17.7



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Results: safety

- 263 patients (94.3%) experienced at least one TEAE at DCO.
- 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.

TEAE, Treatment emergent adverse event.

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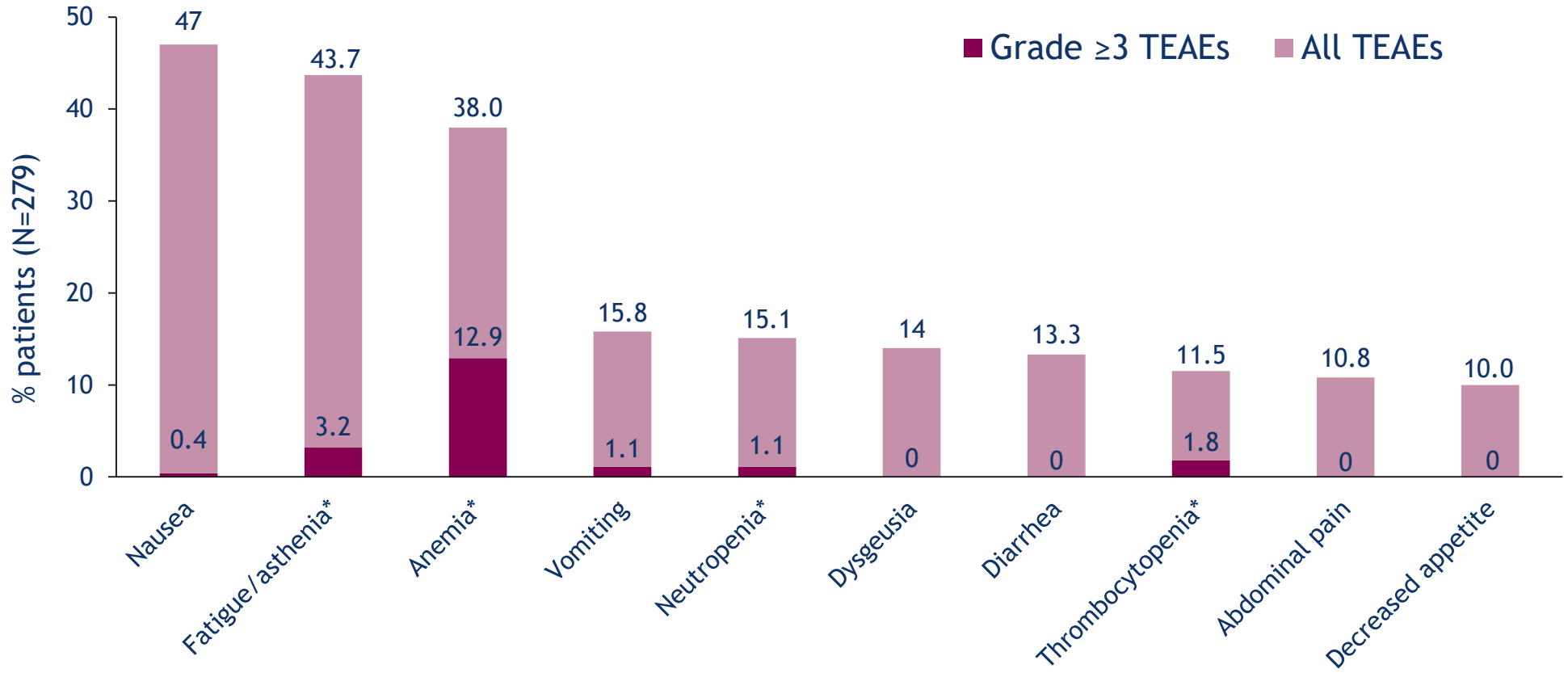
Summary of most common TEAEs (≥10%)



*Grouped-term data.

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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.

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Acknowledgments

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