Survival analysis of NSGO-AVANOVA2/ENGOT-OV24: combination of niraparib and bevacizumab versus niraparib alone as treatment for recurrent platinum-sensitive ovarian cancer. A randomized controlled chemotherapy-free study.

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Background

- Platinum-based chemotherapy is standard treatment for platinum-sensitive recurrent ovarian cancer (PSROC) but is limited by cumulative toxicity
- Phase 3 NOVA: maintenance with niraparib after treatment with platinum-based chemotherapy significantly improved PFS[1] and did not impact sensitivity to subsequent therapy
- Single-arm QUADRA: Niraparib alone is active as definitive treatment for relapsed ovarian cancer[2]
- AVANOVA: Aims to improve PFS by combining PARP inhibition and anti-angiogenic strategies as definitive treatment instead of platinum-based chemotherapy
  - Rationale: tumour hypoxia induced by anti-angiogenic agents results in HRD and enhances the effect of PARP inhibition[1,2]
  - A randomized phase 2 trial showed improved efficacy by combining PARPi with anti-angiogenic therapy[3]
  - AVANOVA1: Phase 1 dose escalation identified a regimen of niraparib 300 mg QD as capsules + bevacizumab 15 mg/kg q3w[4]
  - AVANOVA2: Phase 2 randomized proof of concept study significantly improved progression-free survival (PFS) with the chemotherapy-free regimen of niraparib and bevacizumab compared to niraparib alone, in women with PSROC, regardless of homologous recombination deficiency (HRD) status (MyChoice HRD), duration of chemotherapy-free interval (CFI) and number of previous lines of therapy[5]
- We now present the overall survival (OS) and other efficacy and safety endpoints

HRD = homologous recombination deficiency; PARPi = poly-ADP ribose polymerase; PFS = progression-free survival; QD = once daily; q3w = every 3 weeks

[1]Mirza et al. NEJM 2016; [2]Moore et al. Lancet Oncol 2018; [3]Liu & Matei. Clin Cancer Res 2015; [4]Vergote et al. Proc Natl Acad Sci USA 2015; [5]Liu et al. Ann Oncol 2019; [6]Mirza et al. Cancer Chemother Pharmacol 2019; [7]Mirza MR et al. Lancet Oncol 2019

Trial design

NCT02354131

- High-grade serous/endometrioid PSROC
- Any number of previous lines of therapies
- Measurable/evaluable disease
- Prior bevacizumab permitted

Randomize 1:1

- Niraparib 300 mg QD d1–21
- Niraparib 300 mg QD d1–21 + bevacizumab 15 mg/kg q3w

Until disease progression or toxicity

Stratification factors
- HRD status (positive vs negative)
- Chemotherapy-free interval (6–12 vs >12 months)

Primary endpoint: Investigator-assessed PFS in the Intention-to-Treat population

Patient enrollment and disposition

Randomized (n=97)

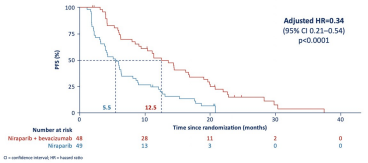
Niraparib + bevacizumab (n=48)	Single-agent niraparib (n=49)
• Evaluable for efficacy and safety (n=48) • Evaluable for PROs (n=47)	• Evaluable for efficacy and safety (n=49) • Evaluable for PROs (n=49)
• Treatment ongoing (n=3) • Both niraparib and bevacizumab discontinued (n=45) – Disease progression (n=32) – Adverse event (n=9) – Other reason (n=4)[a] – Dead from any cause (n=25)	• Treatment ongoing (n=3) • Treatment discontinued (n=46) – Disease progression (n=39) – Adverse event (n=5) – Other reason (n=2)[b] – Dead from any cause (n=29)

PRO = patient-reported outcome. **Performance status deteriorated to 3/4 (n=1), withdrew consent (n=1), Other reason (n=2), [b]Investigator decision (n=1), serious compliance issues (n=1).

Efficacy Endpoints

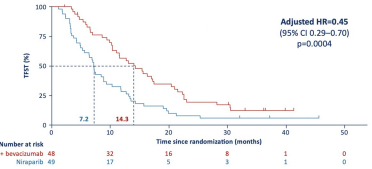
Median follow-up: 24.7 months

Updated PFS (Primary Endpoint) in the ITT Population

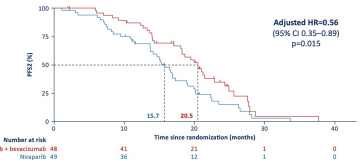


CI = confidence interval; HR = hazard ratio

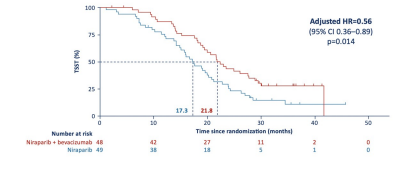
Time to First Subsequent Therapy



Time to Second Progression or Death (PFS2)

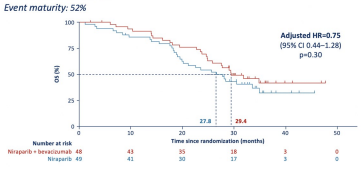


Time to Second Subsequent Therapy



Overall Survival

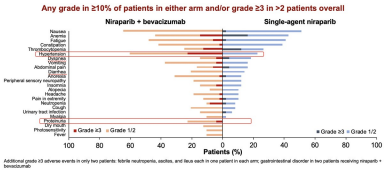
Event maturity: 52%



Summary of Secondary Endpoints

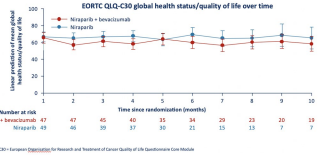
Endpoint	HR (95% CI)	Niraparib + bevacizumab better / Niraparib better	Median, months Niraparib + bevacizumab vs niraparib
PFS	0.34 (0.21–0.54)		12.5 vs 5.5
TFST	0.45 (0.29–0.70)		14.3 vs 7.2
PFS2	0.56 (0.35–0.89)		20.5 vs 15.7
TSST	0.56 (0.36–0.89)		21.8 vs 17.3
OS	0.75 (0.44–1.28)		29.4 vs 27.8

Summary of adverse events



Additional grade ≥3 adverse events in only two patients: febrile neutropenia, ascites, and ileus each in one patient in each arm; gastrointestinal disorder in two patients receiving niraparib + bevacizumab

Patient-reported outcomes



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module

Conclusions

- **NSGO-AVANOVA2 is the first randomized trial to evaluate a chemotherapy-free combination of two established agents approved for use in recurrent ovarian cancer (niraparib and bevacizumab)**
- **Compared with niraparib alone, the combination of niraparib + bevacizumab as definitive treatment for ovarian cancer significantly improved clinical outcome.**
- **Niraparib + bevacizumab combination therapy was well tolerated**
- **No detrimental effect on quality of life was observed**
- **These results support the rationale behind a randomized phase 3 trial to change current standard-of-care therapy**

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