

Time Without Symptoms or Toxicity (TWiST) in patients with newly diagnosed advanced ovarian cancer receiving maintenance olaparib or placebo plus bevacizumab: analysis of PAOLA-1/ENGOT-ov25 Phase III trial

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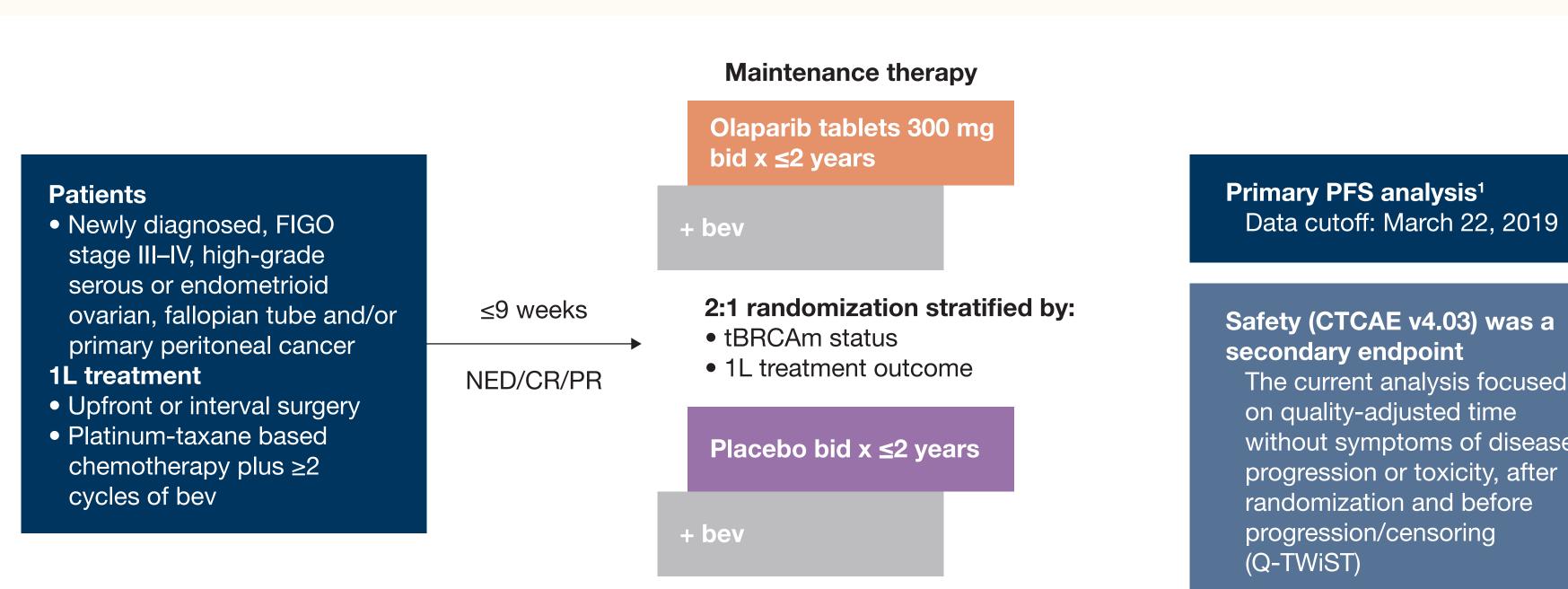
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INTRODUCTION

• In the Phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644),¹ maintenance olaparib plus bevacizumab (bev) provided a significant progression-free survival (PFS) benefit, compared with placebo plus bev, in patients with newly diagnosed advanced ovarian cancer in response after platinum-based first-line (1L) chemotherapy plus bev.¹ A subgroup analysis revealed a substantial PFS benefit in patients who tested postive for homologous recombination deficiency (HRD; BRCA1 and/or BRCA2 mutation [BRCAm] and/or genomic instability; median PFS 37.2 vs 17.7 months) leading to US and EU labels for this combination. We analyzed TWiST in PAOLA-1, using several definitions of toxicity (TOX) and by molecular subgroups.

METHODOLOGY

Figure 1. PAOLA-1 study design



bid, twice daily; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; FIGO, International Federation of Gynecological Oncology; NED, no evidence of disease; PR, partial response; tBRCAm, tumor BRCA mutation, TOX, toxicity.

- The current analysis focused on TWiST, which was defined as the time without symptoms or toxicity after randomization and before disease progression (or censoring for progression).
- Toxicity (TOX) data were obtained from the reported adverse events (AEs), and the TOX state included the total number of days after randomization and before progression spent with significant symptoms or TOX grade ≥ 2 .
- As it is possible for a patient to have more than one type of TOX over time, overlapping TOX intervals were not doubly counted.
- TWiST duration (PFS minus TOX) was presented using Kaplan–Meier curves of TOX and PFS^{2,3}
- The difference between the two treatment groups in median TWiST was calculated and presented associated with its 95% confidence interval (CI).

Definition of significant symptoms or TOX were explored using the following approaches:

1) All grade \geq 2 AEs; 2) all grade \geq 2 AEs with symptoms; 3) all grade \geq 2 AEs selected to be linked to olaparib (fatigue, nausea, vomiting, and anemia).

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).



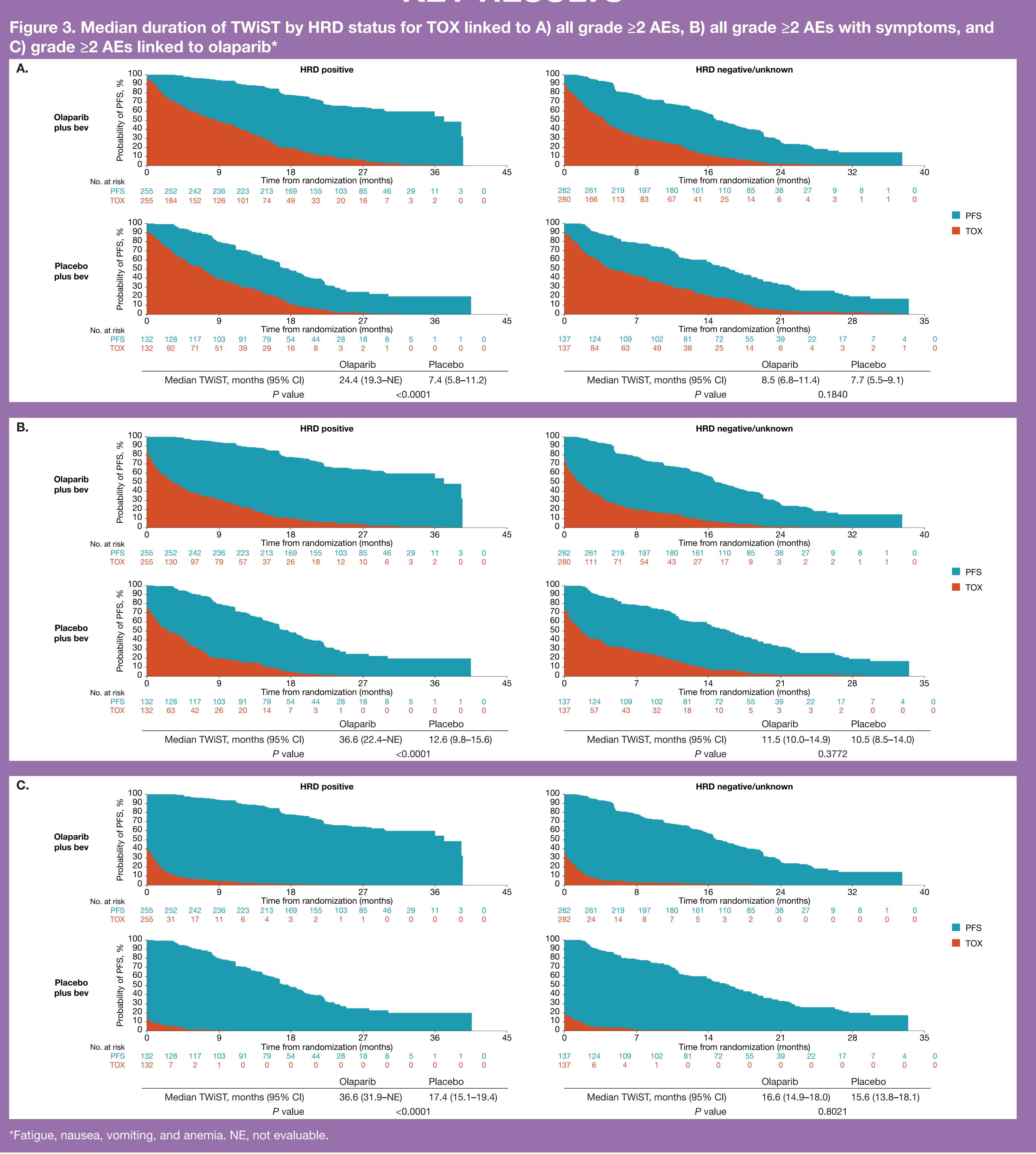








KEY RESULTS



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Figure 2. TWiST a



- therapy.

1. Ray-Coquard I et al. N Engl J Med 2019;381:2416-28. 2. Friedlander M et al. Lancet Oncol 2018;19:1126–34. 3. Friedlander M et al. Lancet Oncol 2021;22:632–42.



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X	TWIST	TOX	TWIST	тох
				PFS1 date
Dura	tion of TOX		Duration of TWIST	

PFS1, time to first progression.

RESULTS IN THE INTENT-TO-TREAT POPULATION

• Median (95% CI) duration of TWiST for all grade ≥ 2 AEs for olaparib plus bev vs placebo plus bev arms was 14.1 months (12.5–16.1) versus 7.7 months (5.9–9.1), respectively; median duration of TWiST for all grade ≥ 2 AEs with symptoms for olaparib plus bev vs placebo plus bev arms was 17.2 months (16.0–20.1) versus 11.3 months (9.7–13.6), respectively.

• Considering only grade ≥ 2 AEs linked to olaparib, median (95% CI) duration of TWiST was 21.9 months (20.2–22.5) versus 16.6 months (14.6–18.0).

CONCLUSIONS

 The efficacy of maintenance olaparib plus bev vs placebo plus bev in patients with newly diagnosed advanced ovarian cancer was supported by a significant TWiST benefit regardless of the definition of TOX, including all grade ≥ 2 AEs, all grade ≥ 2 AEs with symptoms, and all grade ≥ 2 AEs with symptoms linked to olaparib.

• This confirms the clinically meaningful benefit of the combination, most notably in the HRD-positive subgroup, where median TWiST was approximately tripled for all grade ≥ 2 AEs with symptoms.

• TWiST integrating all grade ≥ 2 symptoms is an innovative representation to estimate the potential benefit of maintenance

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