Poster No. 738P

Quality-Adjusted Time Without Symptoms or Toxicity (QA-TWiST) and Quality-Adjusted Progression-Free Survival (QA-PFS) of First-line (1L) Maintenance Niraparib in Patients With Advanced Ovarian Cancer (OC) – Results from the PRIMA Trial

Maria-Pilar Barretina-Ginesta,[1] Bradley J. Monk,[2] Sileny Han,[3] Bhavana Pothuri,[4] Annika Auranen,[5] Dana M. Chase,[2] Domenica Lorusso,[6] Charles Anderson,[7] Sophie Abadie-Lacourtoisie,[8] Noelle Cloven,[9] Elena I. Braicu,[10] Amnon Amit,[11] Andrés Redondo,[12] Ruchit Shah,[13] Nehemiah Kebede,[13] Carol Hawkes,[14] Divya Gupta,[15] Tatia Woodward,[16,*] David M. O'Malley,[17] and Antonio González-Martín,[18] for the PRIMA/ENGOT-OV26/GOG-3012 Investigators

[1]Institut Català d'Oncologia, Girona, Spain; [2]University of Arizona, Creighton University, Phoenix, AZ, USA; [3]University Hospitals Leuven, Leuven, Belgium; [4]Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, NY, USA; [5]Tampere University Hospital; Tampere, Finland; [6]MITO and Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [7]GOG and Willamette Valley Cancer Institute, Eugene, OR, USA; [8]Institut de Cancérologie de l'Ouest (ICO) – Site Paul Papin, Angers, France; [9]Texas Oncology (US Oncology Network), Fort Worth, TX, USA; [10]Campus Virchow Clinic, Charité–Universitätsmedizin Berlin, Berlin, Germany; [11]Rambam Medical Centre, Haifa, Israel; [12]Hospital Universitario La Paz, Madrid, Spain; [13]Open Health Evidence and Access, Bethesda, MD, USA; [14]GlaxoSmithKline, Brentford, UK; [15]GlaxoSmithKline, Waltham, MA, USA; [16]GlaxoSmithKline, Philadelphia, PA, USA; [17]Ohio State University COM – James CCC, OH, USA; [18]Clínica Universidad de Navarra, Madrid, Spain

*Employed by GlaxoSmithKline when research was conducted

Background

- OC, a rare but frequently fatal cancer,[1] is the fifth leading cause of cancer death among women in the USA.[2]
- 1L treatment regimens with platinum-based chemotherapy often result in high response rates, but most patients with advanced disease experience a recurrence.[3]
- Niraparib is a once-daily oral, highly selective PARP-1/2i. In the PRIMA trial, niraparib maintenance treatment significantly prolonged median PFS versus placebo in patients with newly diagnosed advanced OC, regardless of biomarker status (**Box 1**).[4]

Box 1. PRIMA/ENGOT-OV26/GOG-3012 trial (PRIMA)[4]

- Phase 3 (NCT02655016)
- Patients with advanced OC responsive to 1L platinum-based chemotherapy

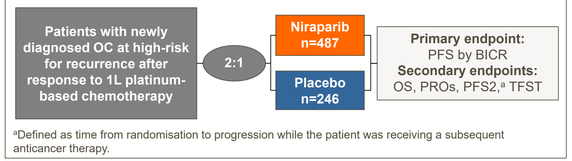
Niraparib vs. placebo	Median PFS, months	HR
HRd population	21.9 vs. 10.4	0.43 (P<0.001)
Overall population	13.8 vs. 8.2	0.62 (P<0.001)

- An effective maintenance therapy is one that delays disease progression without negatively impacting HRQoL through drug toxicity.
- Quality-adjusted PFS (QA-PFS) and quality-adjusted time without symptoms or toxicity (QA-TWiST) are methods that incorporate the quantity of survival and HRQoL to evaluate the benefits of new treatments.
- This post hoc analysis of PRIMA assessed the QA-PFS and the QA-TWiST of patients on maintenance niraparib versus placebo in the overall and HRd populations.

Methods

- PRIMA was a Phase 3, randomised, double-blind, placebo-controlled, multicentre study in adults (aged ≥18 years) with advanced OC (stage III or IV) who had completed six to nine cycles of platinum-based chemotherapy with a physician-assessed complete or partial response.[4]
- Patients were randomised 2:1 to receive maintenance niraparib or placebo once daily in 28-day cycles for 36 months or until disease progression (**Figure 1**).[4]

Figure 1. PRIMA study design



[a]Defined as time from randomisation to progression while the patient was receiving a subsequent anticancer therapy.

- QA-PFS and QA-TWiST were assessed as described in **Table 1** for the overall ITT and HRd populations.
- For all analyses, the level of significance was set to 5%, and CIs were calculated using a non-parametric bootstrap method. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Table 1. Outcome measures of interest

Variable	Role	Operational definition
Mean QA-PFS	Calculated outcome	Product of the PFS function, obtained by restricted mean survival estimation and the mean EQ-5D index score function prior to progression
TOX time, months	Partitioned survival variable	(Area under the Kaplan–Meier curve for days with AEs*) / 30.4375 days
TWiST time, months	Partitioned survival variable	(Area under the Kaplan–Meier curve for days to PFS event) – (area under the Kaplan–Meier curve for days with AEs*) / 30.4375 days
Utility for TOX, U_{TOX}	Utility	Average EQ-5D utilities collected during TOX state in the PRIMA trial
Utility for TWiST, U_{TWiST}	Utility	Assumed to be 1.0
Mean QA-TWiST	Calculated outcome	QA-TWiST = U_{TWiST} × TWiST + U_{TOX} × TOX

QA-PFS adjusts the restricted mean PFS estimate to take into account patient HRQoL as measured by the EQ-5D; TOX was defined as the time before PFS during which patients experienced grade ≥2 AEs of interest*; TWiST was defined as the time without symptoms of disease progression or toxicity; in the PRIMA trial, the estimated utility for the TOX health state using the EQ-5D-5L values was 0.767 and 0.761 for the ITT and HRd populations, respectively.
*Symptomatic AEs that would be expected to substantially impact HRQoL: fatigue or asthenia, nausea, vomiting, abdominal pain and abdominal bloating.

Results

QA-PFS analysis

- Mean QA-PFS was significantly longer with niraparib than with placebo in the overall ITT population, and in the HRd population (**Table 2**).

Table 2. Mean duration of PFS and QA-PFS per study population at last PFS of the treatment group

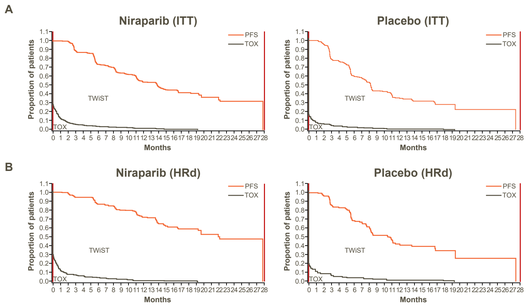
Population	Duration, restricted mean (95% CI), months		
	Niraparib	Placebo	Difference
Overall ITT at 27.8 months[a]	n=487	n=246	
PFS	15.5 (14.3, 16.5)	11.9 (10.2, 13.3)	3.6 (1.8, 5.7)
QA-PFS	14.0 (12.6, 15.0)	9.9 (8.6, 11.0)	4.1 (2.2, 5.8)
HRd at 27.8 months[a]	n=247	n=126	
PFS	19.3 (17.6, 20.7)	13.4 (11.0, 15.1)	5.9 (3.5, 8.7)
QA-PFS	17.7 (15.6, 19.1)	11.2 (9.1, 12.6)	6.5 (3.9, 8.9)

[a]Last PFS of patients randomised to niraparib; patients without an EQ-5D-5L index score were assigned the mean EQ-5D-5L for their treatment arm.

QA-TWiST analyses

- The QA-TWiST analysis for the overall ITT and HRd populations was conducted at the last PFS of patients randomised to niraparib (27.8 months) (**Figure 2**).

Figure 2. Partitioned survival curves for the overall ITT population (A) and the HRd population (B)



Curves show the area under the PFS Kaplan–Meier curves partitioned into two parts: time spent in the TWiST state and time spent in the TOX state. TOX included grade ≥2 AEs of interest (fatigue or asthenia, nausea, vomiting, abdominal pain and abdominal bloating).

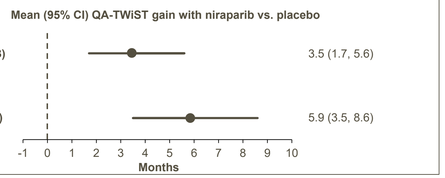
- There was a significantly longer restricted mean time spent in the TWiST, but not TOX, state with niraparib compared with placebo (**Table 3**).
- Patients treated with niraparib had significantly greater mean QA-TWiST compared with placebo in the ITT and HRd populations (**Figure 3**).

Table 3. Restricted mean duration of health states for the overall ITT population and HRd population at last PFS of the treatment group

Population	Restricted mean duration (95% CI), months		
	Niraparib	Placebo	Difference
Overall ITT at 27.8 months	n=487	n=246	
TOX[a]	0.7 (0.5, 0.8)	0.4 (0.2, 0.6)	0.2 (−0.1, 0.6)
TWiST	14.8 (13.6, 16.0)	11.5 (9.8, 12.9)	3.3 (1.5, 5.3)
HRd at 27.8 months	n=247	n=126	
TOX[a]	0.7 (0.4, 1.0)	0.6 (0.2, 1.0)	0.1 (−0.4, 0.6)
TWiST	18.6 (16.9, 20.0)	12.8 (10.6, 14.6)	5.8 (3.5, 8.4)

[a]TOX included grade ≥2 AEs of interest (fatigue or asthenia, nausea, vomiting, abdominal pain and abdominal bloating).

Figure 3. QA-TWiST gain for the overall ITT population and HRd population at last PFS of the treatment group



Conclusions

- In patients with advanced OC, 1L niraparib maintenance treatment was associated with a significant gain in QA-PFS compared with placebo, indicating a patient-relevant improvement in PFS.
- Niraparib increased restricted mean PFS without significantly increasing TOX time (duration of symptomatic grade ≥2 AEs prior to disease progression). The significant gain in TWiST demonstrates that niraparib-treated patients remained symptom-free for longer than those who received placebo.
- Collectively, the significant gains in QA-PFS and QA-TWiST demonstrate that niraparib maintenance treatment is associated with a PFS improvement whilst preserving patients' HRQoL.

Abbreviations

1L, first-line; ADP, adenosine diphosphate; AE, adverse event; BICR, blinded independent central review; CI, confidence interval; EQ-5D(-5L), EuroQol 5-dimension questionnaire (5-level version); HR, hazard ratio; HRd, homologous recombination deficiency; HRQoL, health-related quality of life; ITT, intention-to-treat; OC, ovarian cancer; OS, overall survival; PARP-1/2i, poly (ADP-ribose) polymerase-1/2 inhibitor; PFS, progression-free survival; PFS2, progression-free survival 2; PRO, patient-reported outcome; QA-PFS, quality-adjusted progression-free survival; QA-TWiST, quality-adjusted time without symptoms or toxicity; TFST, time to first subsequent treatment; TWiST, time without symptoms of disease recurrence or toxicity.

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