Real-World Overall Survival in Second-Line Maintenance Niraparib Monotherapy vs Active Surveillance in Patients With Recurrent Ovarian Cancer

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Background

- Ovarian cancer (OC) is one of the leading causes of gynecological cancer-related deaths worldwide.[1,2]
- Patients with advanced disease often relapse and require multiple lines of chemotherapy.[3]
- Second-line (2L) treatments typically include platinum-based regimens for patients with platinum-sensitive disease; however, survival tends to decrease with each subsequent line of therapy.[3]
- Niraparib is an oral poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) 1/2 inhibitor that has demonstrated improved progression-free survival (PFS) in the 2L maintenance (2Lm) setting in patients with recurrent OC in the NOVA trial, while maintaining a consistent safety profile.[4]
  - NOVA (NCT01847274) was a randomized, double-blind, placebo-controlled Phase 3 trial assessing the efficacy of niraparib maintenance for patients with platinum-sensitive recurrent OC; PFS was the primary endpoint and overall survival (OS) was a secondary endpoint.[5]

Aim

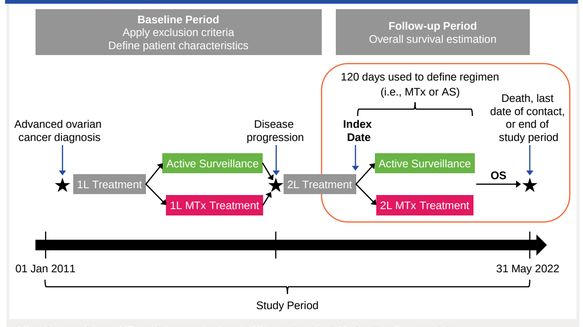
The aim of this real-world study was to compare OS in breast cancer gene wild-type (*BRCA*wt) patients with recurrent OC who received niraparib 2Lm monotherapy or were under active surveillance (AS) to complement NOVA trial results.

Methods

Study design

- This analysis used the US nationwide Flatiron Health de-identified electronic health record–derived longitudinal database. The database consists of patient-level structured and unstructured data, curated via technology-enabled abstraction.[6,7]
- The study included patients diagnosed with OC including peritoneal and fallopian tube cancers during the study period (01 Jan 2011 to 31 May 2022) from approximately 280 cancer clinics (~800 sites of care) (**Figure 1**).
- The index date was defined as the end of 2L non-maintenance therapy.

Figure 1. Study design



AS, active surveillance; MTx, maintenance treatment; OS, overall survival; 1L, first line; 2L, second-line.

Cloning approach

- A target trial emulation cloned inverse probability of censoring weighting (IPCW) methodology was used for this study and was selected *a priori* to minimize measurable confounding, immortal-time (e.g., when the start of follow-up and treatment initiation do not coincide), and selection biases.[8]
  - Baseline patient characteristics were reported for each cohort prior to cloning.
- Balance of key baseline covariates between the two cohorts was assessed using standardized mean differences with a threshold of <15%.
- The methods of this approach are described in further detail by Perhanidis et al. ICPE 2023 (abstract submitted).

Data outcomes and analyses

- Follow-up was measured from the index date until last activity, death, or end of study period, whichever came first.
- Median OS was assessed with IPCW Kaplan-Meier curves and hazard ratios (HR) were estimated from IPCW Cox regression models with a robust variance estimate to account for within-subject correlation.

Study population

- Patients were included based on section criteria described in **Table 1**.

Results

- Overall, 199 and 707 *BRCA*wt patients received niraparib 2Lm or were under AS, respectively **(Table 1)**.

Table 1. Study population attrition

Selection criteria, N (%)	Total recurrent OC patients	2Lm	2L AS
Patients diagnosed with OC* from 1 Jan 2011 to 31 May 2022 (study period)	10,394 (100)		
– had an initial diagnosis prior to 31 May 2021	9688 (93.2)		
– with evidence of epithelial histology	9146 (88.0)		
– received 2 prior lines of therapy	4220 (40.6)		
– were ≥18 years at the index date and did not initiate any type of 2Lm during a predefined 120-day grace period with the exception of 2Lm niraparib monotherapy maintenance	2953 (28.4)		
– had an index date between 1 Jan 2017 and 2 Mar 2022	1706 (16.4)		
– had at least 1 day of follow up after index date	1542 (14.8)		
– had clinical activity within 90 days of initial diagnosis	1273 (12.2)		
– did not receive 1L or 2L PARP inhibitor as non-maintenance monotherapy treatment (including niraparib). Excluded patients with niraparib 2Lm who did not have a non-cancelled medication order for niraparib	1174 (11.3)	266	908
***BRCA*wt (final population), n**	**906 (8.7)**	**199**	**707**

*Based on the presence of international classification of disease (ICD) version 9 and 10 codes for ovarian, fallopian tube, and/or peritoneal cancer (ICD-9: 183x, 158x; ICD-10: C56x, C57.0x, C48x) with ≥2 documented clinical visits.
AS, active surveillance; *BRCA*wt, breast cancer gene wild-type; OC, ovarian cancer; PARP, poly (adenosine diphosphate [ADP]–ribose) polymerase; 1L, first line; 2L, second line; 2Lm, 2L maintenance.

Baseline characteristics

- Across the niraparib 2Lm and AS cohorts, 26.6% and 29.6% of patients were aged ≥75 years, 30.7% and 22.2% identified their race as other than White, and the majority had Stage III/IV disease (79.9% and 78.6%), respectively (**Table 2**).

Table 2. Patient characteristics before adjustment

	2Lm (N=199)	2L AS (N=707)
Characteristics, n (%)		
Age		
18–74	146 (73.4)	498 (70.4)
≥75	53 (26.6)	209 (29.6)
Race		
White	132 (66.3)	508 (71.9)
Black	9 (4.5)	42 (5.9)
Other	52 (26.1)	115 (16.3)
NR	6 (3.0)	42 (5.9)
Region of residence*		
Midwest	20 (10.1)	76 (10.7)
South	107 (53.8)	308 (43.6)
West	22 (11.1)	94 (13.3)
Northeast	17 (8.5)	73 (10.3)
Other/ Unknown	33 (16.6)	156 (22.1)
Practice type		
Community	168 (84.4)	574 (81.2)
Academic	18 (9.0)	118 (16.7)
Both	13 (6.5)	15 (2.1)
Epithelial Histology		
Serous	156 (78.4)	545 (77.1)
Other	20 (10.1)	68 (9.6)
Epithelial NOS/NR	23 (11.6)	94 (13.3)
ECOG performance status score		
0–1	167 (83.9)	505 (71.4)
2–4	18 (9.0)	93 (13.2)
NR	14 (7.0)	109 (15.4)
Stage at initial diagnosis		
I–II	21 (10.6)	77 (10.9)
III	103 (51.8)	353 (49.9)
IV	56 (28.1)	203 (28.7)
NR	19 (9.5)	74 (10.5)
HRD		
HRd	10 (5.0)	38 (5.4)
HRp	7 (3.5)	56 (7.9)
NR	182 (91.5)	613 (86.7)
Median duration between end of 1L and start of 2L, months (IQR)	13.6 (7.6, 20.9)	6.2 (2.1, 12.5)

*Patients from academic practice types have unknown region in the database. Due to rounding of decimals percentages in some categories may not equal 100%
AS, active surveillance; ECOG, Eastern Cooperative Oncology Group; HRD, homologous recombination deficiency; HRd, HR deficient; HRp, HR proficient; IQR, interquartile range; NOS, not otherwise specified; NR, not reported; 1L, first line; 2L, second line; 2Lm, 2L maintenance.

Treatments received and follow-up

- After the index date, 65.3% (n=130) of 2Lm niraparib and 73.8% (n=522) of AS patients received at least one more line of therapy (LOT); of which 20.6% (n=41) and 23.2% (n=164) of patients received ≥3 LOTs, respectively.
- Median follow-up (interquartile range) was 15.6 (9.1, 27.1) and 9.3 (3.2, 21.0) months for niraparib 2Lm and AS cohorts, respectively.

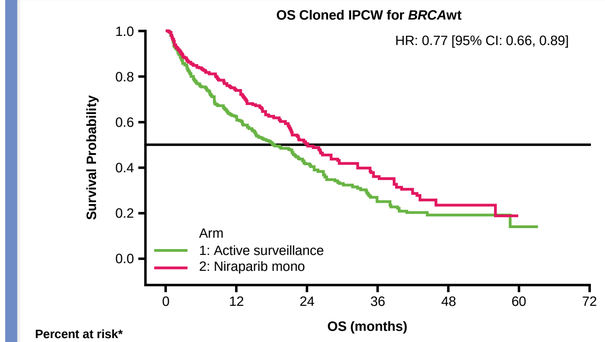
Target trial emulation clone-IPCW

- Balance was achieved with standardized differences <15% on key variables that may impact treatment decisions, including;
  - Age group, race, region of residence, practice type, histology, Eastern Cooperative Oncology Group status, disease stage, and duration between end of 1L and start of 2L treatment.

Overall survival

- This Median OS was 24.1 (95% confidence interval [CI]: 20.9, 29.5) and 18.4 (95% CI: 15.1, 22.8) months for niraparib 2Lm and AS cohorts, respectively (HR: 0.77 [95% CI: 0.66, 0.89]) (**Figure 2**).
- At 24 months, survival rates (95% CI) were 50.6% (42.5, 58.1) for patients in the niraparib 2Lm cohort and 41.6% (35.4, 47.6) for patients in the AS cohort.

Figure 2. IPCW Kaplan-Meier curves



*Percent at risk is reported in percentages due to the cloning and weighting approach which can result in non-whole numbers.
*BRCA*wt, breast cancer gene wild-type; IPCW, inverse probability of censoring weighting; NR, not reported; OS, overall survival.

Conclusions

- This real-world study included an older and more diverse patient population than typically included in randomized controlled trials.
- Based on the IPCW emulated trial, the median OS in niraparib 2Lm cohort was 5.7 months greater than the AS cohort.
  - This real-world study provides informative data on OS outcomes in patients with *BRCA*wt OC receiving niraparib 2Lm versus AS from the Flatiron Health database.
  - Homologous recombination deficiency testing in the real world is limited and prevented examination of *BRCA*wt + HR-deficient subgroup. In addition, data distinguishing between germline and somatic *BRCA* mutations were not available; therefore, conclusions can only be made for *BRCA*wt patients.

Disclosures

KNM reports consulting fees from Aravive, AstraZeneca, Alkemeres, Addi, Blueprint Pharma, Clovis, Elevar, Eisai, Genentech/Roche, GSK/Tesaro, Hengrui, ImmunoGen, Imab, Merck, Mersana, Myriad, Novartis, Lilly, Mereo, OncXerna, OncoNova, Verastem, Sorrento, and VBL Therapeutics; research funding from Lilly, Merck, Verastem, and PTC Therapeutics; and serves on Board of Directors for Gynecologic Oncology Group F and is Associate Director for Gynecologic Oncology Group Partners. **JP** is an employee of GSK and holds stock/shares at Boston Scientific. **LK and AG** are employees of GSK. **NMZ** is an employee of GSK and reports stocks and shares in GSK. **RLC** reports advisory role fees (AbbVie, Aravive, AstraZeneca, Clovis Oncology, Eisai, Genentech/Roche, GSK, Janssen, Merck, Novocure, OncoMed/Mateo, OncoQuest, OncoSec) and research funding (AbbVie, Genmab, V Foundation).

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