The Use of Real-World Evidence From the Edinburgh Ovarian Cancer Database to Explore a Data Gap in the PRIMA Trial

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Background

Niraparib is a once-daily oral, highly selective poly(ADP-ribose) polymerase (PARP)-1 and PARP-2 inhibitor indicated as maintenance therapy in all patients with newly-diagnosed advanced epithelial high-grade ovarian, fallopian tube or primary peritoneal cancer following response to first-line (1L) platinum-based chemotherapy (CT)[1,2]

Niraparib significantly improved progression-free survival (PFS) in the Phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial in patients with newly-diagnosed advanced ovarian cancer (OC) who had responded to platinum-based CT[3]

The intention-to-treat population in PRIMA included patients with OC who had primary or interval debulking surgery (PDS/IDS)

- Patients with Stage III OC post-IDS were included irrespective of residual disease, and patients with Stage III OC post-PDS were included with visible residual disease (VRD) only; patients with Stage IV OC were included irrespective of surgery type and residual disease (VRD or no VRD [NVRD])
- Therefore, a data gap exists with respect to outcomes in patients with Stage III OC post-PDS NVRD

Objectives

The objectives of this study were to 1) estimate the size of the Stage III OC post-PDS NVRD population and 2) to identify the magnitude of the difference in overall survival (OS) and PFS outcomes between patients with Stage III OC post-PDS NVRD and the rest of the advanced OC population, using real-world evidence (RWE) from the Edinburgh Ovarian Cancer Database

Methods

A retrospective observational study was performed using the Edinburgh Ovarian Cancer Database at the Edinburgh Cancer Centre and Nicola Murray Centre for Ovarian Cancer Research (UK), which contains data collected since 1982 for >4,000 patients with OC[4]

- The database includes prospectively entered information as part of routine clinical care of patients with pathologically confirmed OC. The data cover diagnosis, baseline variables (including age, Eastern Cooperative Oncology Group performance status [ECOG PS], cancer antigen [CA]-125 level, International Federation of Gynaecology and Obstetrics [FIGO] tumour stage, and histologic subtype), treatment, debulking status, and outcome

Baseline characteristics and long-term outcomes were analysed for patients diagnosed with advanced OC between 1 January 2000, and 31 December 2015. Patients were followed until their last patient record or end of study observation period (1 January 2019) (**Figure 1**)

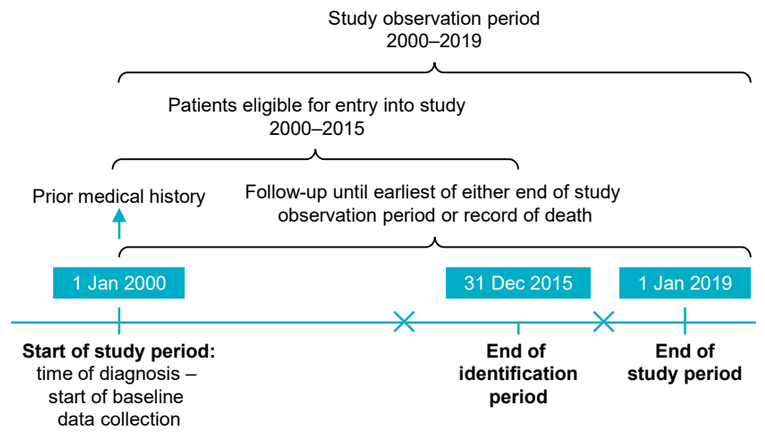
- Eligible patients had histologically confirmed, advanced (FIGO Stage III/IV) high-grade serous or high-grade endometrioid ovarian, fallopian tube or primary peritoneal cancer. Patients with known progressive disease or stable disease after completion of 1L platinum-based chemotherapy were excluded. Identified patients were chosen to match the following three populations:
  - Simulated PRIMA (S-PRIMA) cohort: Stage III VRD after PDS, Stage III after IDS, and Stage IV OC
  - Simulated Stage III NVRD after PDS (S-NVRD after PDS) cohort: Stage III NVRD after PDS
  - Simulated Broad (S-Broad) cohort: aligned to niraparib marketing authorisation as monotherapy for maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer with response following 1L platinum-based CT (included patients irrespective of type and outcome of surgery)

The main outcomes were OS and PFS

- OS was defined as time from diagnosis until death
- PFS was defined in the database as time from diagnosis to first progression as defined by radiology, tumour marker (CA-125) or assessment of the treating physician when other investigations were not evaluable/available

Statistical analyses were performed using R v3.5.1 or above. Baseline characteristics were summarised descriptively, and survival analyses were performed using Cox proportional hazards regression models

Figure 1. Study design



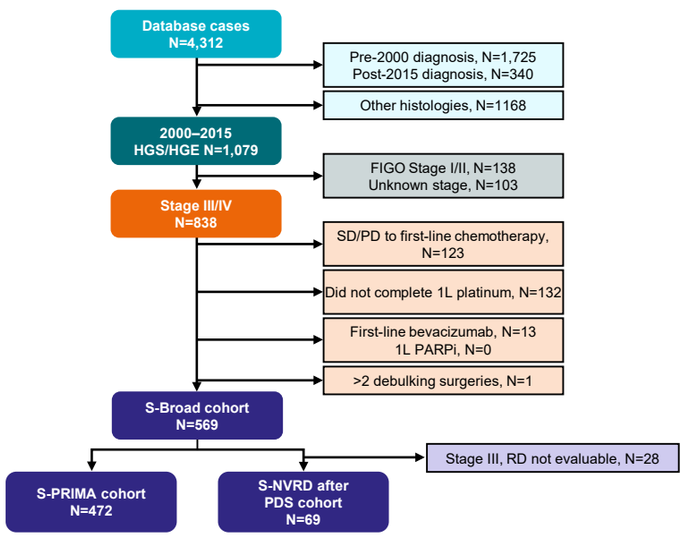
Results

Patient population

A total of 472 and 69 patients met criteria for the S-PRIMA and S-NVRD after PDS cohorts, respectively (**Figure 2**); the S-broad cohort of 569 patients comprised these two cohorts plus 28 patients with Stage III non-evaluable debulking status

Patient demographics and baseline characteristics in the three cohorts were similar to those in the PRIMA trial (**Table 1**)[4]

Figure 2. Patient case flow diagram



1L, first line; FIGO, International Federation of Gynaecology and Obstetrics; HGS/HGE, high-grade serous/high-grade endometrioid; PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease; PDS, primary debulking surgery; RD, residual disease; S-Broad, simulated Broad cohort; S-NVRD after PDS, simulated Stage III no visible residual disease after primary debulking surgery cohort; S-PRIMA, simulated PRIMA cohort, SD, stable disease.

Table 1. Patient demographics and baseline characteristics

Characteristic	S-PRIMA cohort (n=472)	S-NVRD after PDS cohort (n=69)	S-Broad cohort (n=569)
Age at diagnosis, median years (range)	64 (28–87)	60 (39–86)	64 (28–87)
Histological subtype			
HGS	461 (97.7)	61 (88.4)	550 (96.7)
HG endo	11 (2.3)	8 (11.6)	19 (3.3)
Documented primary site			
Ovary	355 (75.2)	64 (92.8)	440 (77.3)
Fallopian tube	3 (0.6)	4 (5.8)	8 (1.4)
Peritoneum	76 (16.1)	1 (1.4)	82 (14.4)
Fallopian tube/ovary	38 (8.1)	0	39 (6.9)
FIGO stage at diagnosis*			
IIIA	5 (1.1)	17 (24.6)	22 (3.9)
IIIB	25 (5.3)	20 (29.0)	48 (8.4)
IIIC	296 (62.7)	32 (46.4)	352 (61.9)
III NS	4 (0.8)	0	5 (0.8)
IV	142 (30.1)	0	142 (25.0)
Germline *BRCA* status			
BRCA mutated	24 (5.1)	6 (8.7)	36 (6.3)
BRCA wild type/VUS	167 (35.4)	29 (42.0)	204 (35.9)
Untested	281 (59.5)	34 (49.3)	329 (57.8)
ECOG PS†			
0	71 (23.5)	18 (42.9)	93 (25.8)
1	140 (46.4)	17 (40.4)	164 (45.4)
2	66 (21.9)	7 (16.7)	78 (21.6)
3	25 (8.3)	0	26 (7.2)
NA	170 (-)	27 (-)	208 (-)
Surgery type			
PDS	323 (68.4)	69 (100)	413 (72.6)
IDS	149 (31.6)	0	156 (27.4)
Residual disease†			
NVRD	66 (14.3)	69 (100)	135 (25.4)
VRD	397 (85.7)	0	397 (74.6)
NA	9 (-)	0	37 (-)
Vital status at last follow-up			
Alive	61 (12.9)	27 (39.1)	94 (16.5)
Dead	411 (87.1)	42 (60.9)	475 (83.5)
Median follow-up from diagnosis, years (95% CI)	10.97 (8.19–13.90)	8.98 (4.97–NC)	10.47 (8.13–13.20)
Median OS from diagnosis, years (95% CI)	2.71 (2.48–3.09)	6.84 (4.11–7.67)	3.07 (2.78–3.39)
Median PFS from diagnosis, years (95% CI)	1.20 (1.14–1.25)	2.45 (1.69–3.51)	1.26 (1.21–1.33)
Median follow-up from simulated randomisation, years (95% CI)	10.40 (7.53–13.40)	8.42 (4.37–NC)	9.87 (7.53–12.70)
Median OS from simulated randomisation, years (95% CI)	2.03 (1.77–2.31)	6.20 (3.48–7.05)	2.30 (2.06–2.68)
Median PFS from simulated randomisation, years (95% CI)	0.46 (0.43–0.54)	1.94 (1.11–2.90)	0.55 (0.47–0.63)

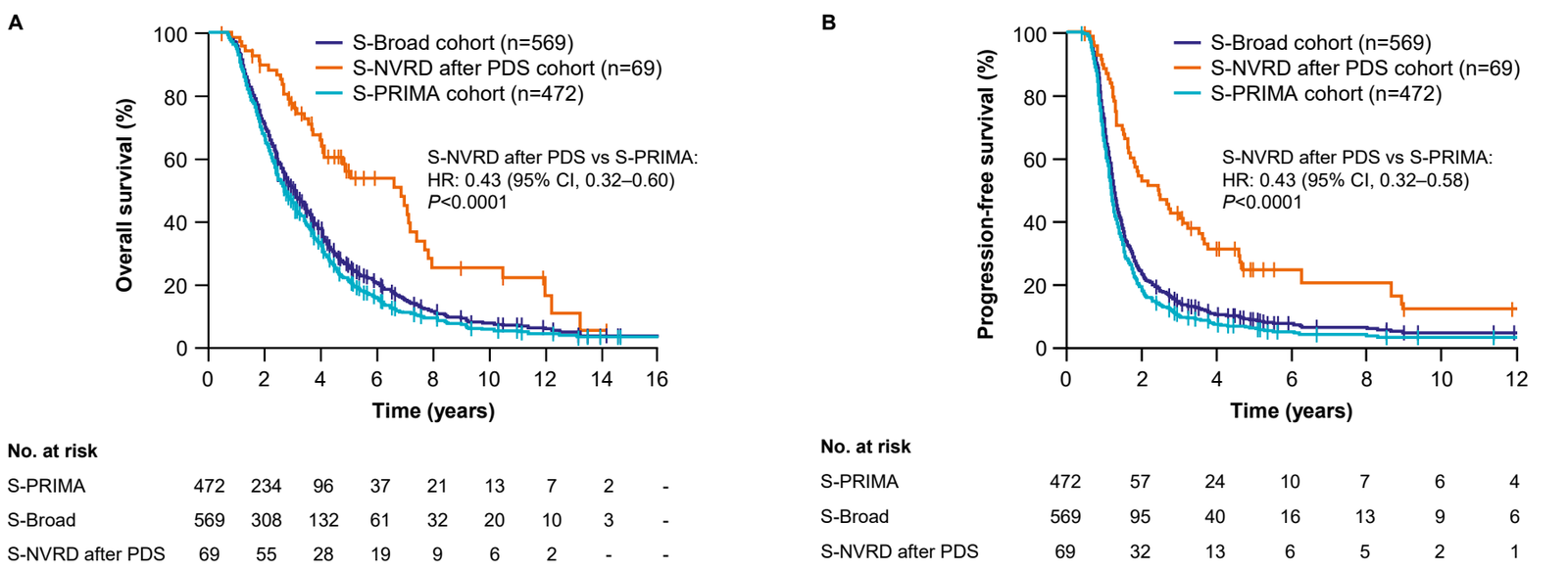
Values are number of patients (%) unless specified otherwise.
*Pre-2014 FIGO stages most likely used for database as latest diagnoses were 2015; †percentages are for the proportion of patients with available status.
BRCA, breast cancer gene; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynaecology and Obstetrics; HG endo, high-grade endometrioid; HGS, high-grade serous; IDS, interval debulking surgery; NA, not assessed; NS, nonspecific; NVRD, no visible residual disease; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; S-Broad, simulated Broad cohort; S-NVRD after PDS, simulated Stage III no visible residual disease after primary debulking surgery cohort; S-PRIMA, simulated PRIMA cohort; VRD, visible residual disease; VUS, variant of unknown significance.

OS and PFS

There was statistically significantly (P<0.0001) longer OS and PFS in the S-NVRD after PDS cohort compared with in the S-PRIMA cohort (**Figure 3**)

The S-Broad cohort demonstrated survival curves above the S-PRIMA curves (OS hazard ratio [HR]: 0.88 [95% confidence interval (CI), 0.77–1.00], P=0.0556; PFS HR: 0.86 [95% CI, 0.76–0.98], P=0.0244), indicating improved outcomes (**Figure 3**)

Figure 3. Kaplan–Meier curves for A) OS and B) PFS in the S-PRIMA, S-NVRD after PDS and S-Broad cohorts

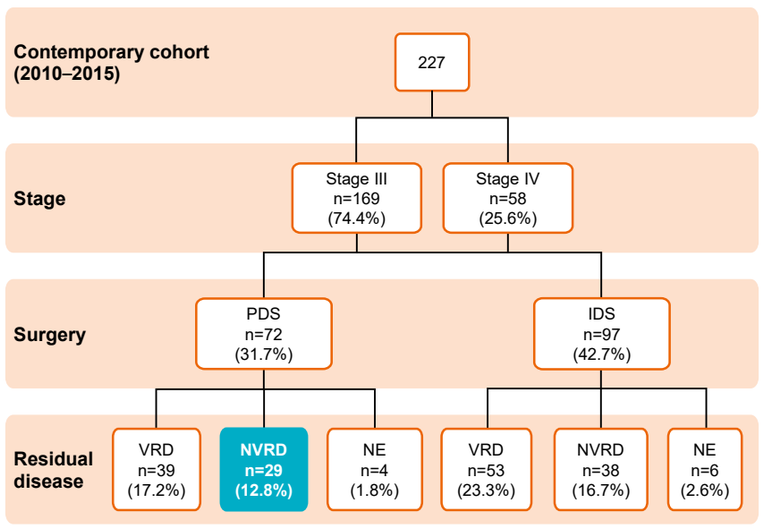


CI, confidence interval; HR, hazard ratio; NVRD, no visible residual disease; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; S-Broad, simulated Broad cohort; S-NVRD after PDS, simulated Stage III no visible residual disease after primary debulking surgery cohort; S-PRIMA, simulated PRIMA cohort.

To further assess the difference in survival outcomes between the S-PRIMA and S-Broad cohorts, the database sample was analysed to assess the percentage of patients with Stage III NVRD after PDS included within the S-Broad cohort below

- To further validate the observed patient numbers, a contemporary cohort analysis was conducted among patients in the database diagnosed between 2010 and 2015 (n=227; **Figure 4**):
  - Within this specific contemporary cohort, a total of 169 patients were diagnosed with Stage III disease and 58 patients with Stage IV disease
  - Overall, 42.7% of patients had Stage III disease and IDS and 31.7% had Stage III disease and PDS
  - In this cohort, 17.2% of patients had Stage III disease and VRD after PDS and 12.8% of patients had Stage III disease and NVRD after PDS (1.8% were not evaluable for residual disease)

Figure 4. Contemporary cohort disease characteristics



IDS, interval debulking surgery; NE, non-evaluable; NVRD, no visible residual disease; PDS, primary debulking surgery; VRD, visible residual disease

Conclusions

- Approximately 12% of the S-Broad population was made up of patients with Stage III OC with NVRD after PDS, who have a more favourable prognosis than other patients in the S-Broad cohort
  - The proportion of patients within the Stage III OC with NVRD after PDS population was consistent over time at this UK centre; the contemporary cohort (diagnosis 2010–2015) population of 12.8% was similar to the 12% observed with 16 years of follow-up
- As expected, this analysis confirmed that patients with Stage III OC with NVRD after PDS have significantly better survival outcomes (HR: 0.43; P<0.0001; for both OS and PFS) compared with the S-PRIMA cohort
- The S-Broad cohort showed improved survival outcomes compared with the S-PRIMA cohort, particularly for PFS (P=0.0244), demonstrating that the S-PRIMA cohort consisted of patients with more severe disease than the S-Broad cohort

Implications for Field of OC

Complete resection (NVRD) after primary surgery for Stage III patients is associated with improved outcomes

Despite this positive outcome to surgery, relapse may still occur

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Disclosures

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