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Suggested title: **Maintenance treatment for recurrent ovarian carcinoma – evidence supporting the efficacy and safety of PARP inhibitors**

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Abstract: While recent advances in treatment mean that women with ovarian cancer are living longer, many eventually experience disease relapse highlighting the need for new treatments which can extend progression-free survival (PFS). The PARP inhibitors olaparib, niraparib, and rucaparib, have been approved by the FDA and EMA and are currently available for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Here we review the efficacy and safety data from the key clinical trials supporting these approvals, for second-line maintenance treatment including Study 19, SOLO2/ENGOT-OV21 (olaparib), NOVA/ENGOT-OV16 (niraparib), and ARIEL3 (rucaparib). Across trials, PFS was improved with PARP inhibitor maintenance treatment vs placebo in patients with a *BRCA* mutation. However, evidence from some of the trials shows that a wider group of patients can benefit from PARP inhibitor maintenance treatment including those with or without homologous recombination deficient (HRD) tumours. The safety profile for olaparib, niraparib and rucaparib was generally similar across trials with haematological and gastrointestinal adverse events and fatigue/asthenia being the most common. As evidenced by the significant improvements in PFS and manageable safety profiles in these trials, PARP inhibitors represent a new standard of care for recurrent ovarian cancer in the following platinum-based therapy and delays the need for further chemotherapy.

Keywords: *BRCA* mutation, homologous recombination deficiency, maintenance treatment, niraparib, olaparib, PARP inhibitor, recurrent ovarian carcinoma, rucaparib

Introduction

Worldwide, ovarian cancer is the 7th most common cancer and the 8th most common cause of cancer death in women.[1] The Globocan study estimated there were 239,000 new cases in 2012 and 152,000 deaths due to this disease. There are nearly 600,000 women living within 5 years of an ovarian cancer diagnosis.[1] In the European Union, age-adjusted ovarian cancer mortality rates decreased 10% between 2002 and 2012, to 5.2 per 100,000. The decline for this time period was 16% in the USA, to 4.9 per 100,000 in 2012.[1], however, for the same duration, the prevalence of the disease has increased, with a sharp increase in recent years (Figure 1).[2-4] This increase in prevalence may be attributable to advances in ovarian cancer treatment which leads to more lines of treatment being given to prolong survival without increasing the rate of cure. Because the majority of patients with

advanced ovarian cancer eventually relapse, there is a substantial need for new treatments. One potential strategy to reduce the likelihood of recurrence is to use maintenance therapy after chemotherapy to extend the response to treatment and delay the next line of chemotherapy. Because such extended treatment is difficult to achieve with chemotherapy due to cumulative toxicities, other maintenance therapies are needed.

Poly(ADP-ribose) polymerase (PARP) inhibitors are an intriguing new class of therapeutic agents for ovarian cancer. Inhibition of PARP enzymes slows or abolishes the repair of single-strand breaks in DNA and leads to the formation of double-strand breaks.[5] Double-strand breaks in DNA are normally rectified through the homologous recombination repair (HRR) pathway.[6-8] In cells with homologous recombination deficiency (HRD) such as those with a mutation in *BRCA*1 or *BRCA*2 (*BRCA)*, double-strand breaks cannot be efficiently repaired, resulting in cell death via a process termed 'synthetic sickness' or 'synergistic lethality'.[9] A therapeutic response to PARP inhibitors has been shown in patients with ovarian tumours with mutations in *BRCA* or other HRR genes (e.g. *RAD51*, *BARD1*, *PALB2* and others), and in ovarian tumours with high loss of heterozygosity (LOH), a genomic signature associated with HRD.[10-21] However, clinical evidence has emerged showing that patients with ovarian cancer can also receive clinical benefit from PARP inhibitors regardless of their assay-determined HRD status.[10,11]

Three PARP inhibitors, olaparib (Lynparza®, AstraZeneca), niraparib (Zejula®, Tesaro Inc.), and rucaparib (Rubraca®, Clovis Oncology, Inc.) have shown promising results when used as maintenance treatment of recurrent platinum-sensitive ovarian cancer after completion of platinum-based chemotherapy.[9-11,13,22-24] In the US, each of these agents has FDA approval in this setting.[25-27] Similarly, in Europe, olaparib, niraparib and more recently, rucaparib are now approved for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial response) to platinum-based chemotherapy.[28,29] Olaparib is also approved for use in the treatment setting of recurrent ovarian cancer occurring in germline *BRCA* (*gBRCA*) mutation carriers who have had 3 or more prior lines of therapy in the US,[26] and rucaparib is approved for use for the treatment setting of recurrent ovarian cancer following 2 prior lines of therapy and carrying a germline *BRCA* mutation or in whom a somatic *BRCA* (*sBRCA*) mutation is documented in both the US and Europe.[27,29]

This review summarises the findings from the pivotal clinical trials of olaparib, niraparib and rucaparib results supporting their use as maintenance therapy for recurrent ovarian cancer (ROC).

We highlight the key differences in the clinical trial designs and examine the distinct efficacy and safety profiles of each PARP inhibitor.

Key clinical trial data supporting poly(ADP-ribose) polymerase inhibitors as maintenance treatments for ROC

PARP inhibition as maintenance therapy for ROC has been investigated with olaparib in Study 19 and SOLO2/ENGOT-OV21,[13,15] niraparib in NOVA/ENGOT-OV16,[10] and rucaparib in ARIEL3[11] (see end of text for study name definitions). Because of the different designs and patient populations studied, results from these trials are not directly comparable. For example, in NOVA the primary endpoint was blinded independent central review (BICR)-assessed PFS, whilst in Study 19 and ARIEL3 the primary endpoint was investigator-assessed PFS. Furthermore Study 19 and ARIEL3 all examined the primary endpoint in prospectively defined populations that included all patients whereas NOVA prospectively analysed PFS in distinct subgroups of patients based on the presence/absence of a *gBRCA* mutation and SOLO2 was limited to women carrying a germline or somatic mutation in *BRCA1/2*. Notably, in NOVA patients with a *sBRCA* mutation were included in the non-*gBRCA* cohorts, which is unique to this study.[10] Differences in the patient populations for each study include the proportion of patients with a germline or somatic *BRCA* mutation (Study 19, 51%; SOLO2, 97%; NOVA, 45%; ARIEL3, 35%).[10,11,13,15] While the Phase 3 NOVA and ARIEL3 trials of niraparib and rucaparib, respectively, included all-comers, the only all-comer data for olaparib in the maintenance setting comes from the randomised Phase 2 trial, Study 19. The proportion of patients with a complete response to prior platinum also differed across studies (Study 19, 45%; SOLO2, 46%; NOVA, 51%; ARIEL3, 34%).[10,11,13,15] In contrast to NOVA, enrolment in SOLO2 and ARIEL3 was not limited by target lesion size for patients with a partial response to previous platinum and thus these trials recruited more patients with bulky residual disease (>2 cm) at baseline (SOLO2, 15%; ARIEL3, 19%).[10,11,13,15] An overview of study designs and endpoints for these trials is given in Table 1, key efficacy data are provided in Figures 2 and 3, and a summary of safety data is provided Figure 4. It should be noted that the presentation of data from different studies in these figures is for interest only; the studies included populations with different mutation profiles and had differing inclusion/exclusion criteria and so the results are not directly comparable.

Olaparib

Study 19 was a randomised, Phase 2 evaluation of olaparib capsules (400 mg BID) used as a maintenance treatment of patients (n=265) with platinum-sensitive ROC.[13] The primary endpoint was investigator-assessed PFS from randomisation, which was significantly longer with olaparib than

placebo (median 8.4 months vs 4.8 months; hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.25–0.49; p<0.001; Figure 2A). This advantage was seen across all subgroups that were evaluated (*BRCA* mutation status, age, race [White/non-Jewish], baseline response, and time to progression on penultimate platinum-based regimen). A retrospective analysis of investigator-assessed PFS according to BRCA status completed after publication of the trial showed that median PFS in the subgroup with *BRCA* mutations (*gBRCA* and *sBRCA*; approximately 50% of the women) for olaparib vs placebo was 11.2 months vs 4.3 months (HR, 0.18; 95% CI, 0.10–0.31; Figure 2A). In the subgroup with wild-type *BRCA* (*wtBRCA*), median PFS was 7.4 months vs 5.5 months (HR, 0.54; 95% CI, 0.34–0.85; Figure 2A).[14] For the secondary endpoint of time to progression according to Response Evaluation Criteria In Solid Tumours version (RECIST) 1.1[30] or cancer antigen 125 (CA-125) level (which ever occurred first), the median was 8.3 months in the olaparib arm compared to 3.7 months in the placebo arm (HR, 0.35; 95% CI, 0.25–0.47).[13] The objective response rate at 24 weeks (a secondary endpoint) was higher with olaparib (12%; 7/57 patients with measurable disease at baseline) than with placebo (4%; 2/48)[13] as was the disease-control rate (secondary endpoint; 53% [72/136] vs 25% [32/129]).[31]

In the overall study population, the most notable AEs were gastrointestinal in nature (nausea [olaparib, 68% vs. placebo, 35%] and vomiting [32% vs. 14%]) but fatigue (49% vs 38%) was also common. Most AEs were low grade but the commonest AEs of grade ≥3 (olaparib vs placebo) included fatigue (7% vs 3%), anaemia (5% vs 1%), back pain (2% vs 0%), diarrhoea (2% vs 2%), nausea (2% vs 0%) and vomiting (2% vs 1%).[13]

In Study 19, health-related quality of life (QoL) was assessed using the Functional Assessment of Cancer Therapy Ovarian (FACT-O) questionnaire total score as well as the Trial Outcome Index (TOI; a subset of 26 FACT-O items) and the FACT-O Symptoms Index (FOSI; a subset of 8 FACT-O items). No significant differences were observed between arms in the rates of score improvement across the TOI (odds ratio [OR], 1.14; 95% CI, 0.58–2.24; p=0.7), FOSI (OR, 1.22; 95% CI 0.60–2.51; p=0.59) and FACT-O (OR, 1.17; 95% CI 0.60–2.27; p=0.65).[32]

A more recent long-term follow-up of OS findings in Study 19 (using 79% data maturity) showed a favourable result for olaparib over placebo for OS (HR 0.73, 95% CI 0.55–0.95, nominal p = 0.021), irrespective of *BRCA1/2* mutation status.[33] However, this study was not designed to show a statistically significant difference in OS; the p values did not meet the preset criterion for significance (p<0. 0095) and therefore the favourable treatment effect reported for OS should only be regarded as descriptive. It is noteworthy that this follow-up showed that 24% of patients received olaparib

maintenance therapy for over 2 years and 11% received this treatment for over 6 years and this includes patients with and without BRCA mutations. This analysis identified no new tolerability signals during long-term treatment and adverse events were generally low grade. The incidence of discontinuations due to adverse events was low (6%).

Further pivotal data supporting olaparib in the maintenance treatment of ROC comes from the Phase 3 SOLO2 study in which patients (n=295) with platinum-sensitive ROC and a *BRCA* mutation were treated with olaparib (n=196, 300 mg tablets BID) or placebo (n=99).[15] Median investigator-assessed PFS (primary endpoint) was significantly longer with olaparib (19.1 months [95% CI, 16.3–25.7]) than with placebo (5.5 months [95% CI, 5.2–5.8]; HR, 0.30; 95% CI, 0.22–0.41; p<0.0001; Figure 2B). In a sensitivity analysis of PFS by BICR, median PFS was also longer with olaparib (30.2 months [95% CI, 19.8–not reached]) than with placebo (5.5 months [95% CI, 4.8–5.6]; HR, 0.25; 95% CI 0.18–0.35; p<0.0001; Figures 2B and 3A). Compared to placebo, olaparib improved outcomes for secondary endpoints including median time to first subsequent therapy or death (TFST; 27.9 months vs 7.1 months; HR, 0.28; 95% CI, 0.21–0.38), median time to second progression or death (PFS2 [a parameter that indicates duration of survival on subsequent therapy following progression on maintenance therapy]; not reached vs 18.4 months; HR 0.50; 95% CI, 0.34–0.72), median time to second subsequent therapy or death (TSST; not reached vs 18.2 months; HR, 0.37; 95% CI, 0.26–0.53), median time to study discontinuation or death (19.4 months vs 5.6 months; HR, 0.31; 95% CI, 0.23–0.42) and median time to earliest progression or death (16.9 months vs 4.9 months; HR, 0.30; 95% CI, 0.23–0.41).[15] Data for the secondary endpoint of OS were immature (24% maturity) with medians not reached for either group (HR, 0.80; 95% CI, 0.50–1.31).[15,34]

A recent analysis of tumour responses in the SOLO-2 study showed an objective response rate (ORR) advantage for patients with measurable disease at baseline treated with olaparib vs placebo.[35] This advantage was apparent for ORR assessed by investigators (odds ratio: 3.52, 95% CI = 1.34–10.59) and when assessed by blinded independent central review (odds ratio: non-evaluable). This same analysis also showed a PFS benefit for patients treated with olaparib vs placebo with either a complete or partial response to platinum-based chemotherapy at baseline. In addition, the analysis determined PFS2 values which revealed long-term benefits of olaparib treatment. This benefit was apparent both for patients with a complete response, (HR:0.41 95% CI: 0.22-0.77) and for patients with a partial response to platinum-based chemotherapy at study entry (HR: 0.57 95%CI: 0.36-0.91).

Most AEs were of grade 1–2 severity, the most common AEs of any grade (olaparib vs placebo) were nausea (76% vs 33%), fatigue/asthenia (66% vs 39%), anaemia (44% vs 8%), vomiting (37% vs 19%)

and diarrhoea (33% vs 20%) (Figure 4A)[15] More frequent AEs of grade ≥3 included anaemia (19 % vs 2%), neutropenia (5% vs 4%) and fatigue/asthenia (4% vs 2%) (Figure 4A) Discontinuations due to AEs occurred in 11% of olaparib-treated and 2% of placebo-treated patients. In SOLO2, four patients (2%) in the olaparib arm and 4 patients (4%) in the placebo arm were reported to have myelodysplastic syndrome or acute myeloid leukaemia. The study showed that that the benefits of olaparib on PFS had no detrimental effect on QoL and the toxicities were mostly low grade and manageable. This was emphasised by further analysis of SOLO2 data showing significant improvement in mean quality adjusted PFS (QAPFS) for olaparib vs placebo: 14.0 vs 7.3 months (difference 6.7; 95% CI, 5.0–8.5; p<0.0001.[36] In addition, there was also a significant improvement in mean duration of time without symptoms of disease or toxicity (TWiST): 15.0 vs 7.7 months (difference 7.3; 95% CI, 4.7–9.0; p<0.0001).[36]

Niraparib

In the Phase 3 NOVA trial (n=553) patients were grouped according to whether they had a *gBRCA* mutation or a non-*gBRCA* mutation (this group also included patients with *sBRCA* mutations) (Table 1). The study also included an analysis that grouped patients by HRD.[10] Here, the HRD-positive group included patients with *sBRCA* mutations or other HRD as determined by the Myriad (Salt Lake City, UT) myChoice HRD test. In the *gBRCA* cohort, BICR-assessed PFS (primary endpoint) for niraparib vs placebo (n=138 and 65, respectively) was 21.0 vs 5.5 months (HR, 0.27; 95% CI, 0.17–0.41; p<0.001; Figure 2C and Figure 3B). In the non-*gBRCA*/HRD-positive subgroup, PFS for niraparib and placebo, respectively, was 12.9 vs 3.8 months (HR, 0.38; 95% CI, 0.24–0.59; p<0.001; Figure 2C). In the overall non-*gBRCA* cohort, median PFS was 9.3 vs 3.9 months (HR, 0.45; 95% CI, 0.34–0.61; p<0.001; Figure 2C). An analysis of BICR-assessed PFS in subgroups based on HRD status indicated that niraparib treatment was superior to placebo across all subgroups (Figure 2C): non-*gBRCA*/HRD-positive/*sBRCA* (n=35 and 12): 20.9 vs 11.0 months (HR, 0.27; 95% CI: 0.08–0.90; p=0.02); non-*gBRCA*/HRD-positive/*wtBRCA* (n=71 and 44): 9.3 vs 3.7 months (HR, 0.38; 95% CI, 0.23–0.63; p<0.001); non-*gBRCA/*HRD-negative (n=92 and 42): 6.9 vs 3.8 months (HR, 0.58; 95% CI, 0.36–0.92; p=0.02).[10,37] Data for secondary endpoints of chemotherapy-free interval (CFI), TFST, PFS2, and overall survival were subsequently reported.[38,39] In the *gBRCA* cohort, niraparib significantly improved median CFI (22.8 months) compared to placebo (9.4 months; HR 0.26; 95% CI, 0.17–0.41). Median CFI was also improved in the non-*gBRCA* cohort (12.7 months vs 8.6 months; HR 0.50; 95% CI, 0.37–0.67). Median TFST was significantly improved vs placebo for the *gBRCA* (21.0 months vs 8.4 months; HR, 0.31; 95% CI, 0.21–0.48) and non-*gBRCA* (11.8 months vs 7.2 months; HR, 0.55; 95% CI, 0.41–0.72) cohorts. Though data were immature (*gBRCA*, 30%; non-*gBRCA*, 50%) PFS2 was longer with niraparib than

placebo (*gBRCA*: HR 0.48; 95% CI, 0.242-0.687; non-*gBRCA*: HR 0.69; 95% CI, 0.494–0.964). Less than 20% of OS events had occurred in the overall patient population, but analysis showed a non-significant improvement with niraparib vs placebo (HR 0.73; 95% CI, 0.48–1.13).[38,39]

In the NOVA trial, the most frequent AEs of any grade with niraparib vs placebo were nausea (74% vs 35%), thrombocytopenia (61% vs 6%), fatigue/asthenia (59% vs 41%), anaemia (50% vs 7%), constipation (40% vs 20%), vomiting (34% vs 16%), neutropenia (30% vs 6%) (Figure 4B). The most common grade ≥3 AEs with niraparib vs placebo were thrombocytopenia (34% vs 1%), anaemia (25% vs 0%), neutropenia (20% vs 2%), fatigue/asthenia (8% vs 1%), and hypertension (8% vs 2%) (Figure 4B). These were managed by modifying or delaying the niraparib dose. With niraparib, 15% of patients discontinued treatment due to an AE compared with 2% with placebo. Myelodysplastic syndrome or acute myeloid leukaemia were reported by five patients (1%) in the niraparib arm and 2 (1%) in the placebo arm.[10]

In an analysis of QoL for patients in NOVA, mean pre-progression EQ-5D-5L scores were similar between the niraparib and placebo arms in both the *gBRCA* (0.838 vs 0.834) and non-*gBRCA* (0.833 vs 0.815) cohorts.[40] At baseline, common symptoms related to QoL included fatigue, pain, nausea, vomiting, bloating, and cramps as assessed by the Functional Assessment of Cancer Therapy–Ovarian Symptoms Index (FOSI) questionnaire. These symptoms generally remained stable or improved for patients in the niraparib arm, with the exception of nausea which showed an increase at cycle 2 but declined towards baseline levels thereafter.[40] A more recent analysis of NOVA study data found that mean TWiST for patients receiving niraparib was 2.95 years for patients with *gBRCA* mutations compared with 1.34 years for patients without *gBRCA* mutations.[41,42] Niraparib treatment of these patient groups produced PFS benefits of 3.23 years and 1.44 years, respectively and mean toxicity times of 0.28 years and 0.11 years, respectively. Quality of life was found to remained stable through niraparib treatment and the pre-progression period compared with placebo

Rucaparib

ARIEL3 was a randomised Phase 3 trial (intent-to-treat [ITT] population, n=564) to assess the efficacy and safety of rucaparib as maintenance treatment (600 mg BID, n=375) vs placebo (n=189).[11] Patients with high-grade, platinum-sensitive ovarian carcinoma were required to have shown an objective response to second-line or later platinum-based chemotherapy. A novel aspect of this trial was the prospective validation of the next-generation sequencing (NGS) assay performed in collaboration with Foundation Medicine to identify tumours with high genomic loss of heterozygosity (LOH). In ARIEL3, a cutoff of ≥16% for high LOH was prospectively selected based on

the results of a planned post hoc analysis of data from a prior Phase 2 study, ARIEL2.[16] In the analysis of ARIEL2 data, a cutoff of ≥16% improved median PFS in the LOH-high subgroup compared to the prespecified ≥14% cutoff (7.2 months vs 5.7 months). The HR for PFS was also improved with the ≥16% cutoff (0.51 [95% CI, 0.34–0.74] vs 0.62 [95% CI, 0.42–0.90]).[16]

The design of the ARIEL3 study involved a prospectively defined step-down statistical procedure of three nested cohorts.[11] Firstly, the *BRCA*-mutant cohort (n=196) consisted of 130 patients with *gBRCA* mutations (n=82 and 48 for rucaparib and placebo, respectively), 56 patients with *sBRCA* mutations (n=40 and 16), and 10 patients with unknown *gBRCA* or *sBRCA* status (n=8 and 2). Secondly, the HRD cohort (n=354) included the *BRCA*-mutant cohort and a further 158 patients with *wtBRCA* and high LOH (n=106 and 52). Thirdly, the ITT population (n=564) consisted of the HRD cohort with an additional 161 patients with *wtBRCA* and low LOH (n=107 and 54) and 49 patients with *wtBRCA* and indeterminate LOH (n=32 and 17).

The primary endpoint of ARIEL3 (investigator-assessed PFS) showed a significant benefit for rucaparib in each of the three cohorts. The median PFS in patients with *BRCA*-mutant carcinoma was 16.6 months for rucaparib vs 5.4 months for placebo (HR, 0.23; 95% CI, 0.16–0.34; p<0.0001; Figure 2D). Median investigator-assessed PFS also showed significant advantages for rucaparib over placebo in patients with HRD carcinoma 13.6 months for rucaparib vs 5.4 months for placebo (HR, 0.32; 95% CI, 0.24–0.42; p<0.0001) and in the ITT population, investigator-assessed PFS was 10.8 months for rucaparib and 5.4 months for placebo (HR, 0.36; 95% CI, 0.30–0.45; p<0.0001). Median BICR-assessed PFS for patients with *BRCA*-mutant carcinoma was 26.8 months vs 5.4 months (HR, 0.20; 95% CI, 0.13–0.32; p<0.0001; Figure 3C); for patients with HRD it was 22.9 months vs 5.5 months (HR, 0.34; 95% CI, 0.24–0.47; p<0.0001) and for all patients in the ITT population it was 13.7 months vs 5.4 months (HR, 0.35; 95% CI, 0.28–0.45; p<0.0001; Figure 2D).[11] A pre-planned subgroup analysis found that rucaparib provided a PFS benefit in all clinical subgroups compared with placebo regardless of time to progression on penultimate platinum treatment, response to last platinum treatment, having a bulky lesion (>2 cm) at baseline and having measurable disease at baseline.[11] Investigator-assessed PFS was also significantly longer with rucaparib compared with placebo in patients with wt*BRCA*/LOH-high carcinomas (median 9.7 months vs 5.4 months, respectively; HR, 0.44; 95% CI, 0.29–0.66; p<0.0001) and in patients with wt*BRCA*/LOH-low carcinomas (median 6.7 months vs 5.4 months, respectively; HR, 0.58; 95% CI 0.40–0.85; p=0.0049; Figure 2D). Overall survival (OS) data from the ARIEL3 study are currently immature.[11]

An exploratory analysis of investigator-assessed ORR in patients with measurable disease showed superiority for rucaparib over placebo for all three cohorts in ARIEL 3 (Table 2). These included significant ($p<0.05$) improvements over placebo for measures of ORR evaluated by RECIST. Among rucaparib-treated patients, there were also substantial improvements over placebo in terms of conversion from a partial to a complete response.[11]

In ARIEL3, the most common treatment-emergent AEs of any grade (rucaparib vs placebo) were nausea (75% vs 37%), fatigue/asthenia (69% vs 44%), dysgeusia (39% vs 7%), anaemia (37% vs 6%), constipation (37% vs 24%), vomiting (37% vs 15%), increased alanine or aspartate aminotransferase concentration (ALT/AST) (34% vs 4%), and diarrhoea (32% vs 22%) (Figure 4C). Treatment-emergent AEs of grade ≥3 were reported in 56% of patients in the rucaparib group vs 15% in the placebo group. The most notable and frequent of these were: anaemia (19% vs 1%), increased ALT/AST (10% vs 0%), fatigue/asthenia (7% vs 3%), neutropenia (7% vs 2%), thrombocytopenia (5% vs 0%), and nausea (4% vs 1%) (Figure 4C).[11] Discontinuations due to an AE (excluding disease progression) occurred in 13% and 2% of patients, respectively. Myelodysplastic syndrome or acute myeloid leukaemia were reported in three patients (1%) receiving rucaparib, of these, two had *gBRCA*-mutant carcinoma and one had *wtBRCA*/LOH low carcinoma, and no patients in the placebo arm. Overall, the safety findings showed that rucaparib was well tolerated and AEs were manageable; they were mainly low grade and the incidence of more serious events declined after initial cycles of treatment.

In an analysis of the secondary endpoint of time to worsening on the disease-related symptoms–physical subscale of the FOSI-18 questionnaire, no significant difference was noted between the rucaparib and placebo arms in the *BRCA*-mutant cohort (HR, 1.24; 95% CI, 0.82–1.86).[11] An analysis of patient-centred outcomes in the ARIEL 3 study has recently reported that mean QAPFS was significantly longer for patients treated with rucaparib-compared with placebo (12.02 vs 5.74 months) and that in patients with *wtBRCA*, mean QAPFS was longer for rucaparib than placebo regardless of LOH status.[43] Mean quality-adjusted TWiST (Q-Twists) analysis using all grade ≥3 treatment-emergent adverse events was significantly longer for rucaparib than placebo (ITT population, 13.32 vs 6.44 months) and for patients with a BRCA mutation (16.42 vs 6.68 months, respectively). Additional patient-reported outcomes are expected to be published in the future.

Discussion

For women with platinum-sensitive ovarian cancer, PARP inhibitor maintenance treatment constitutes a new standard of care that can delay the need for further chemotherapy. In key clinical

trials, olaparib, niraparib and rucaparib maintenance treatment notably increased PFS for patients with ROC following a response to second- or later-line platinum-based chemotherapy.[10,11,13,15] As might be expected, in these trials, PARP inhibitors were effective in patients with ROC and *BRCA* mutations. In non-*gBRCA* patients enrolled in NOVA and in patients with *wtBRCA* in ARIEL3, niraparib and rucaparib, respectively, were also effective in patients with HRD.[10,11] However, while both of these studies found that PFS was improved in patients with tumours associated with HRD there are distinct differences in the methods used to classify patients with HRD. In NOVA, the HRD status of tumours was evaluated using the myChoice HRD test and the HRD-positive group in the primary analysis included patients with an *sBRCA* mutation.[10] An exploratory analysis in NOVA did show a benefit for patients with *wtBRCA* and HRD (*sBRCA* not included). ARIEL3 examined LOH as a biomarker for HRD and in an exploratory analysis of patients with *wtBRCA* and high LOH, PFS was improved with rucaparib vs placebo.[11] Furthermore, in both studies patients without a *BRCA* mutation or HRD demonstrated improvement in PFS, indicating that neither *BRCA* status nor HRD is a sufficiently precise biomarker to predict which patients will benefit from PARP inhibitor maintenance treatment.[10,11] The FDA and EMA approvals for olaparib, niraparib, and rucaparib use as second-line maintenance therapy of ROC do not specify *BRCA* mutation type or HRD status.[25-27]

These studies have also demonstrated the benefits of PARP inhibitor maintenance treatment in addition to extension of PFS. In ARIEL3, rucaparib treatment led to a higher ORR than placebo with a number of patients with a partial response converting to a complete response on study.[11] In SOLO2, there were also notable advantages in ORR for olaparib compared with placebo in patients with measurable disease at baseline.[35] Thus in some patients not only is progression delayed, or even prevented, they may have a deepening of response following maintenance therapy with a PARP inhibitor. The SOLO2, NOVA and ARIEL 3 studies assessed secondary endpoints including CFI, TFST, PFS2, and TSST (first used in Study 19 as exploratory endpoints).[15,38,39,44,45] PARP inhibitor maintenance treatment produced improvements in these endpoints in these studies providing further evidence that these drugs are suited to maintenance therapy in which the objective is to delay the need for additional therapy. Furthermore, the results also suggest that PARP inhibitor treatment does not affect the efficacy of subsequent lines of treatment.[15,38,39] For OS, an analysis of all patients in Study 19 showed that olaparib maintenance treatment resulted in a small but non-significant improvement over placebo (29.8 months vs 27.8 months, respectively), with the largest improvement observed in patients with a *BRCA* mutation (34.9 months vs 30.2 months, respectively).[45] A notable minority of patients in this study appear to be long-term survivors with

11% receiving olaparib treatment for over 6 years. OS data for the Phase 3 studies are currently immature.[10,11,15]

The safety and tolerability findings in the pivotal maintenance studies indicate that olaparib, niraparib, and rucaparib have somewhat similar AE profiles.[10,11,13,15] Many AEs appear to be class effects of PARP inhibitors, such as haematological AEs (e.g., anaemia, thrombocytopenia, neutropenia), gastrointestinal AEs (e.g., nausea, vomiting), and fatigue/asthenia. In general, the majority of AEs were low grade and/or transient and were managed with treatment interruption, dose reductions, and/or supportive care (e.g., transfusions, antiemetic medications). Discontinuation rates associated with AEs were also similar across trials and were generally higher in the PARP inhibitor arms than in the placebo groups.[10,11,13,15]

Notable differences in the AE profiles include a higher incidence of any grade and grade ≥3 haematological AEs, particularly thrombocytopenia, with niraparib compared with olaparib and rucaparib. An exploratory analysis of the NOVA trial (RADAR), identified two significant parameters that could be used to predict the need for niraparib dose modification.[46,47] These were a baseline body weight of <77 kg and/or baseline platelet counts of <150,000/µl. It is critical that these criteria are monitored and the dose of niraparib is adjusted to improve tolerability. In response to these findings, a protocol amendment was made in the ongoing PRIMA study which permitted starting dose reductions in patients with low body weight or platelet counts.[48] The impact of this modification has recently been reported to be a significant decrease in grade ≥3 haematologic and non-haematologic toxicities and an approximately 80% reduction in grade 4 thrombocytopenia and platelet transfusions.[49] With olaparib, niraparib and rucaparib it is necessary to monitor full blood counts at baseline and during subsequent treatment due to the reported incidence of myelosuppression and thrombocytopenia.[23,25-27] Hypertension (any grade and grade ≥3) was also observed more frequently with niraparib than with olaparib and rucaparib. Niraparib's effect on hypertension is believed to be linked to its pharmacological inhibition of the dopamine transporter, norepinephrine transporter and serotonin transporter.[50] Niraparib requires monthly monitoring for hypertension during the first year and periodically thereafter during treatment.[25,50] With rucaparib, the incidence of any grade elevations in AST/ALT was higher than reported with olaparib or niraparib. These increases were transient and not associated with criteria for drug-induced hepatotoxicity.[11] Some of the other differences in the AEs observed may be reflective of the specific PARP enzymes that each drug can target; all three inhibit PARP1 and PARP2 but their actions against other PARPs are variable.[23,51,52] Olaparib, niraparib and rucaparib have been reported to increase levels of serum creatinine.[25-29,53] This is believed to be a PARP inhibitor class effect resulting from

inhibition of creatinine transporters in the kidney but not a result of acute kidney injury.[23,54,55] The exact consequences of the variable toxicity of the PARP inhibitors have not been entirely elucidated and may warrant further investigation.

Based on available data from Study 19, SOLO2, NOVA, and ARIEL3 maintenance treatment with a PARP inhibitor did not have a detrimental impact on QoL for patients with ROC.[11,32,36,40] An evaluation of patients in SOLO2 even demonstrated that olaparib maintenance treatment resulted in a longer period in which patients did not experience disease symptoms or toxicity compared to patients receiving placebo, emphasizing another advantage of PARP inhibitor maintenance therapy for patients with ROC.[36]

The pivotal studies have demonstrated the utility of PARP inhibition as maintenance treatment following second-line or later platinum-based chemotherapy. In the future, it will be of interest to determine if these, or other PARP inhibitors, could be effectively used earlier in ovarian carcinoma maintenance treatment. The recent SOLO-1 Phase 3 study (n=391) investigated the use of olaparib as first-line maintenance treatment in patients with newly diagnosed advanced ovarian carcinoma and germline (n=388) or somatic (n=2) *BRCA*1/2 mutations.[56,57] The results show very substantial benefits of PARP inhibitor treatment of ovarian carcinoma over placebo after a median 41 months of follow-up.[57] The risk of disease progression or death was 70% lower with olaparib than with placebo. The adverse event profile was consistent with the known toxic effects of olaparib. These results indicate the potential of PARP inhibitors as first-line maintenance therapy. A similar Phase 3 randomised study, PRIMA (n=630),[48] in which niraparib is being as assessed vs placebo as treatment for stage III or IV ovarian cancer in patients who showed a response to front-line platinum-based chemotherapy, has completed recruitment and the efficacy results are awaited.

Future directions

As use of PARP inhibitors increases and indications expand to allow earlier use, their roles in the treatment of ovarian cancer and sequencing of use relative to other anticancer agents will need to be evaluated. For instance, cross-resistance between PARP inhibitors might be circumvented due to the different PARP enzymes targeted by these therapies, suggesting that a 'PARP-after-PARP' strategy may be suitable for patients who have not responded to one of these drugs or has initially responded but then progressed.[58,59] This strategy could involve patients who have either stopped PARP treatment after progression or who have stopped after a defined period, for example following first line therapy, without progression. One approach that is being investigated in the OReO study (NCT03106987, n=416) is that patients with ovarian carcinoma who originally responded to

platinum-based therapy and subsequently progressed on a PARP inhibitor are then switched to olaparib treatment. Patients recruited to this study will have received different previous treatments. Many, for example will have originally received olaparib and are re-treated with the same drug after further platinum-based chemotherapy. As PARP inhibitors are being introduced earlier in the pathway of treatment research strategies are needed to explore the effects of re-treatment at a later date. Sequencing in relation to other widely used treatments for ovarian cancer will also require examination as most available data currently comes from trials performed in the second line or later.

The utility of PARP inhibitors in the maintenance setting for ROC may be improved by combining them with other agents that have different mechanisms of action such as those that interfere with DNA replication and repair pathways (e.g. ATR, ATM, CHK1/2 and WEE1. [60,61] For example, antiangiogenic agents (e.g., bevacizumab) induce chronic hypoxia in tumours, which induces a down-regulation of *BRCA1* and *RAD51*, leading to HRD although this effect is controversial.[62] Thus tumours with hypoxia-induced HRD may be sensitive to PARP inhibition. This effect was also shown in a recent study using mouse tumour xenografts in which cediranib treatment resulted in sensitivity to olaparib by producing hypoxia which suppresses the expression of the HDR factors BRCA1/2 and RAD51 recombinase (RAD51).[63,64] However, cediranib also had a direct effect on HDR, independent of its ability to induce tumour hypoxia. This effect was specific to tumour cells and suggested that DNA repair could be manipulated to induce synergistic lethality.

Combination with checkpoint inhibitors (e.g., nivolumab [anti-PD-1]) is another strategy as tumours with HRD express high levels of novel, tumour-specific protein sequences, which can attract PD-L1–expressing tumour-infiltrating lymphocytes.[65] Preclinical studies have shown that rucaparib combined with an anti-PD-1 inhibitor improved anti-tumour activity in a *BRCA* deficient mouse model.[66] Several studies of PARP inhibitors in combination with other agents in patients with ovarian cancer are currently being conducted or are nearing completion. These include: PAOLA-1 (NCT 02477644, Phase 3, randomised controlled trial - maintenance olaparib with bevacizumab), OVARIO (NCT03326193, Phase 2, randomised trial - maintenance niraparib with bevacizumab), ATHENA (NCT03522246, Phase 3, randomised trial - maintenance rucaparib with nivolumab),[67-69] There is also the ongoing VELIA study (NCT02470585, Phase 3 trial in previously untreated advanced ovarian cancer, randomised to one of three regimens: carboplatin/paclitaxel plus veliparib then veliparib maintenance or carboplatin/paclitaxel plus placebo then placebo maintenance or carboplatin /paclitaxel plus veliparib then placebo maintenance).

An open-label trial involving PARP inhibitors in combination with other treatments for ovarian cancer was the JAVELIN OVARIAN PARP 100 (NCT03642132, avelumab with chemotherapy then maintenance with avelumab and talazoparib) was recently terminated due to futility after another similar study, the JAVELIN OVARIAN 100 failed to meet its primary endpoint.[70] A further open label trial is the ongoing Phase 3, FIRST study (NCT03602859), in which patients are treated with first-line platinum-based chemotherapy with TSR-042 [dostarlimab, anti-PD-1 monoclonal antibody] and niraparib).). An alternative combination approach is being taken in the ongoing ENGOT-OV46/AGO/DUO-O trial (NCT03737643, planned n=927). This is a Phase 3 randomised, placebo-controlled study in which patients with newly diagnosed advanced ovarian cancer will all initially receive durvalumab in combination with chemotherapy and bevacizumab. This will be followed by randomisation to maintenance durvalumab and bevacizumab or maintenance durvalumab, bevacizumab and olaparib; PFS will be the primary endpoint. An additional study of interest is the ENGOT-OV43/BGOG trial (NCT03740165, planned n=1,000) in which patients with ovarian cancer will initially receive a single 3-week cycle of carboplatin/paclitaxel. Subsequently, they will be randomised to pembrolizumab and olaparib or pembrolizumab and placebo or placebo alone with PFS and OS as the primary endpoints.

Beyond ovarian cancer, the PARP inhibitors have also shown encouraging efficacy in the treatment of a variety of other cancers and are being developed as potential treatments in multiple indications including haematological malignancies, advanced prostate cancer, pancreatic cancer, bladder cancer, triple negative breast cancer, squamous cell lung cancer, non-small cell lung cancer, colorectal cancer, and metastatic melanoma.[71-81] The use of these drugs as maintenance therapy, however, has mostly focused on ROC. Future wider use of the PARP inhibitors as maintenance therapy has the exciting potential to delay progression in many other cancer types.

Conclusion

Overall, the use of PARP inhibitors as maintenance therapy is an important development in delaying disease progression in ROC, and in Study 19 with the longest follow up, about 10% patients have had a sustained response lasting more than 6 years. The findings from these studies justify further investigation of these agents for use as either monotherapy or in combination with other treatments. The PARP inhibitors have differing properties that could be used to provide increased or more suitable treatment options for numerous patients. Greater awareness of these drugs and wider routine application of them in ROC maintenance regimens in the future could improve the prognosis and reduce mortality in this continuingly prevalent and lethal disease in women both with and without *BRCA* mutations.

Study name definitions: ARIEL3: Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy; NOVA: A trial of niraparib for ovarian cancer that has come back after platinum chemotherapy; OReO: Study to examine Olaparib maintenance Retreatment in patients with Epithelial Ovarian cancer; RADAR: Rapid Adjustment of Dose to reduce Adverse Reactions; SOLO-1: Olaparib maintenance monotherapy in patients with *BRCA* mutated ovarian cancer following first line platinum based chemotherapy; SOLO-2: Olaparib treatment in *BRCA* mutated ovarian cancer patients after complete or partial response to platinum chemotherapy; Study 19: randomised, double-blind placebo-controlled Phase 2 study comparing outcomes with olaparib as maintenance therapy in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer.

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Table 1. Key features and differences between designs of pivotal clinical trials on olaparib, niraparib and rucaparib in the maintenance treatment of ovarian carcinoma

Study name	Study 19[13,45] (N=265)	SOLO2/ENGOT-OV21[15] (N=295)	NOVA/ENGOT-OV16[10] (N=553)	ARIEL3[11] (N=564)
Treatments	Olaparib vs placebo (1:1)	Olaparib vs placebo (2:1)	Niraparib vs placebo (2:1)	Rucaparib vs placebo (2:1)
Mutation types	• *gBRCA* (n=96)* • s*BRCA* (n=20)* • *gBRCA/sBRCA* status could not be determined (n=20)* • *wtBRCA* or *BRCA* mutation of unknown significance (n=118)* • *BRCA* mutation status not available (n=11)*	• *gBRCA* (n=286) • *wtBRCA* (n=2) • *BRCA* mutation not confirmed to be deleterious/of unknown significance (n=7)	• *gBRCA* (n=203) • *sBRCA* (n=47) • *wtBRCA/*HRD positive (n=115) • HRD negative (n=134) • HRD not determined (n=54)	• *gBRCA* (n=130) • *sBRCA* (n=56) • *wtBRCA*/high LOH (n=158) • *wtBRCA*/low LOH (n=161) • wtBRCA/LOH indeterminate (n=49)
Prospectively defined analysis groups	• All patients (N=265)	• All patients (N=295)	• *gBRCA* (n=203) • non-*gBRCA* (n=350; includes *sBRCA, wtBRCA/*HRD positive, HRD negative, and HRD not determined) • non-*gBRCA* with HRD (n=162; only *sBRCA* and *wtBRCA/*HRD positive)	• *BRCA* mutant (n=196; includes *gBRCA* and *sBRCA*) • HRD cohort (n=354; includes *gBRCA, sBRCA,* and *wtBRCA*/high LOH) • ITT population (N=564; includes all patients)
Primary endpoint	Investigator-assessed PFS	Investigator-assessed PFS	BICR-assessed PFS	Investigator-assessed PFS

Secondary endpoints	• Time to progression per RECIST or CA-125 level • ORR • Disease-control rate • Percentage change from baseline in size of target tumour • Disease-related symptoms and HRQoL • Safety	• Time to first subsequent therapy or death • PFS2 • Time to second subsequent therapy or death • Time to discontinuation or death • Time to earliest progression or death • OS • Safety and tolerability • HRQoL	• Patient-reported outcomes • Chemotherapy-free interval • Time to first subsequent therapy • PFS2 • Time to second subsequent therapy • OS	• BICR-assessed PFS • Time to worsening in FOSI-18 DRS-P subscale • Time to worsening in FOSI-18 total score • OS • Safety • Population PK modelling
Assessments	• CT scans every 12 weeks • Patient-reported outcomes were assessed using FACTO and FOSI questionnaires • Safety was assessed with AEs, laboratory testing, vital signs, physical examinations	• CT or MRI scans every 12 weeks until week 72, and then every 24 weeks thereafter until objective disease progression; after disease progression, patients were followed every 12 weeks for second progression and survival • Safety was assessed with AEs laboratory testing, vital signs, and physical examinations • HRQoL was assessed using TOI-FACTO questionnaire	• CT or MRI to at baseline, every 8 weeks through cycle 14, and then every 12 weeks until treatment discontinuation • Safety was assessed with AEs, laboratory testing, vital signs, physical examinations • Patient-reported monitoring included FOSI and EQ-5D-5L questionnaires	• CT and/or 'other' imaging every 12 weeks during treatment and after treatment for patients who discontinued for a reason other than progression • Safety assessed with AEs, laboratory testing, vital signs, and physical examinations • FOSI-18 questionnaire (for patient -reported outcomes)
Additional subgroups examined	• *BRCA* mutation status • Age • Jewish or non-Jewish ancestry • Response status at baseline	• Previous bevacizumab • Presence of a confirmed *BRCA* mutation	• Age • Race • Region • Time to progression before enrolment • Bevacizumab use	• Age • Race • Measurable disease at baseline • Bulky disease at baseline • Previous bevacizumab use • No. of platinum regimens

	• Time to progression from the start of penultimate platinum-based regimen		• Best response to platinum • Platinum in last or penultimate therapies • No. of previous platinum regimens • No. prior chemotherapy regimens	• Time to progression of previous platinum regimen • No. of previous chemotherapy regimens • Response to last platinum
Stratification variables	• Time to progression after completion of the penultimate platinum regimen (6–12 months vs ≥12 months) • Best response to last platinum (complete or partial) • Ancestry (Jewish vs non-Jewish)	• Response to previous chemotherapy (complete vs partial) • Length of platinum-free interval (>6–12 months vs ≥12 months)	• Time to progression after completion of the penultimate platinum regimen (6–12 months vs ≥12 months) • Use of bevacizumab in conjunction with penultimate or last platinum regimen • Best response during last platinum regimen (complete or partial)	• Homologous recombination repair gene mutation status (mutation in *BRCA1* or *BRCA2*, mutation in non-*BRCA* gene associated with homologous recombination, or no mutation in *BRCA* or a homologous recombination gene) • Time to progression of penultimate platinum (6–12 months vs ≥12 months) • Best response to last platinum (complete or partial)
Assessment of *BRCA*/HRD	• Case report forms documenting previous local *gBRCA* testing • Retrospective *BRAC* Analysis testing (Myriad Genetics, Salt Lake City UT, USA) for *gBRCA* • Retrospective NGS (Foundation Medicine, Cambridge, MA, USA) for *sBRCA*	*BRAC* Analysis testing (Myriad Genetics, Salt Lake City UT, USA) – assessed *BRCA* mutation only	My Choice HRD test –(Myriad Genetics, Salt Lake City UT, USA)	T5 NGS assay (Foundation Medicine, Cambridge, MA, USA)

In all four studies, patients had platinum-sensitive recurrent ovarian carcinoma.
*Mutation status as reported in updated analysis of Study 19 data.[45]
BICR: blinded, independent central review; CA-125: cancer antigen 125; CT: computer tomography; DRS-P: disease-related symptoms–physical; FOSI-18: National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy Ovarian Symptom Index 18; HRD: homologous recombination deficient; *gBRCA*: germline *BRCA1* or *BRCA2*; HRQoL: health-related quality of life; HRD: homologous recombination repair deficient; HRR: homologous recombination repair; ITT: intent to treat; MRI: magnetic resonance imaging; NGS: next generation sequencing; ORR: objective response rate; OS: overall survival; PFS2: time from randomization until assessment of progression during receipt of the next anticancer therapy after the study treatment or until death; RECIST: Response Evaluation Criteria in Solid Tumours; *sBRCA*: somatic *BRCA1* or *BRCA2*; TOI-FACTO: Trial outcome index derived from the Functional Assessment; *wtBRCA*: wild-type *BRCA1* or *BRCA2*.

Table 2. Exploratory analysis of investigator-assessed objective response rate for patients with measurable disease at baseline in the ARIEL3 study

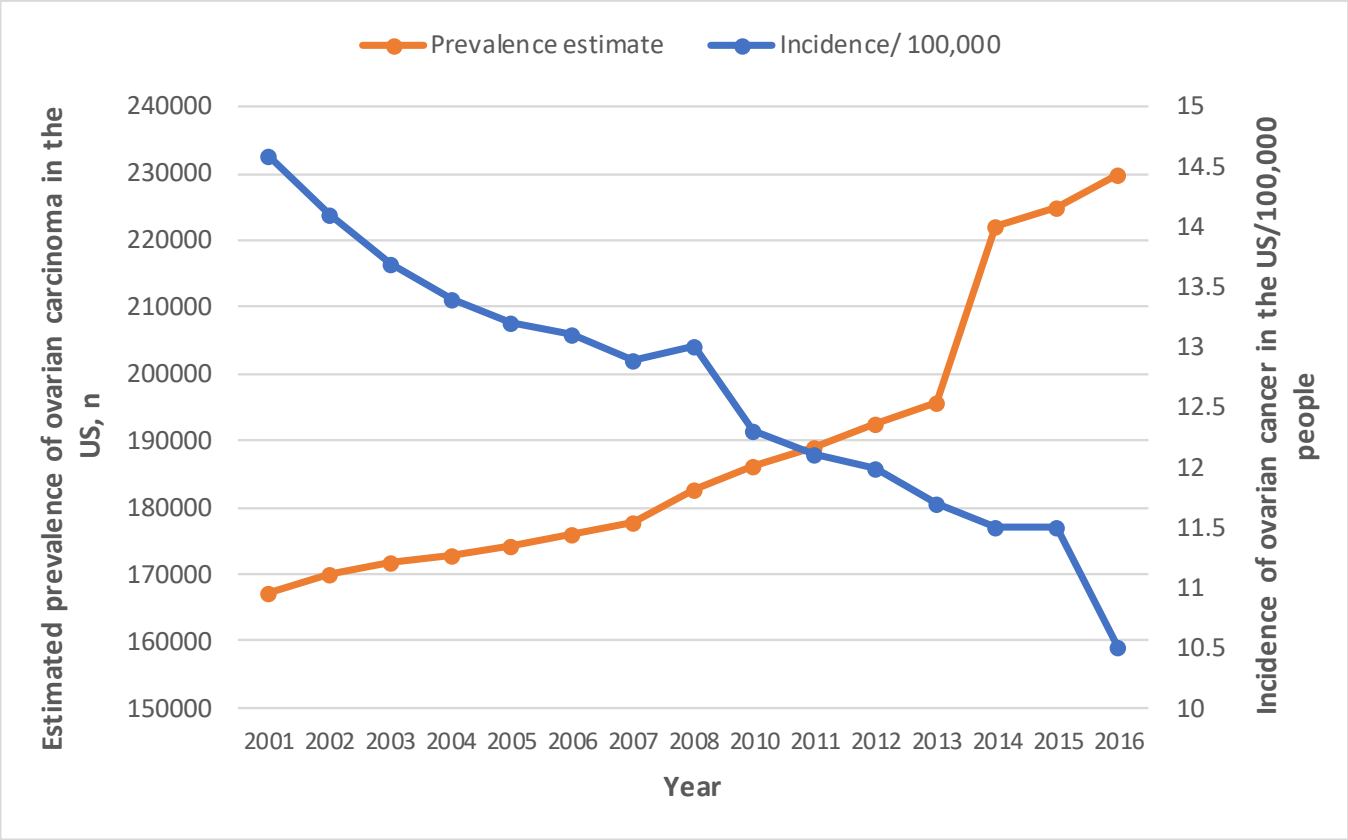
	***BRCA* Mutant**		**HRD**		**ITT**	
	Rucaparib (n=40)	**Placebo (n=23)**	**Rucaparib (n=85)**	**Placebo (n=41)**	**Rucaparib (n=141)**	**Placebo (n=66)**
RECIST ORR %, (n)	37.5* (15)	8.7 (2)	27.1* (23)	7.3 (3)	18.4* (26)	7.6 (5)
Complete response	17.5 (7)	0 (0)	11.8 (10)	0 (0)	7.1 (10)	1.5 (1)
Partial response	20.0 (8)	8.7 (2)	15.3 (13)	7.3 (3)	11.3 (16)	6.1 (4)
Stable disease	47.5 (19)	34.8 (8)	50.6 (43)	41.5 (17)	50.4 (71)	43.9 (29)
Progressive disease	12.5 (5)	56.5 (13)	21.2 (18)	51.2 (21)	27.0 (38)	48.5 (32)
Not evaluable	2.5 (1)	0 (0)	1.2 (1)	0 (0)	4.3 (6)	0 (0)

*Cochrane-Mantel-Haenszel $p<0.05$ vs placebo.

HRD: homozygous recombination deficiency; ITT, intent to treat; ORR, objective response rate; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: Coleman et al 2017 (supplementary material)[11]

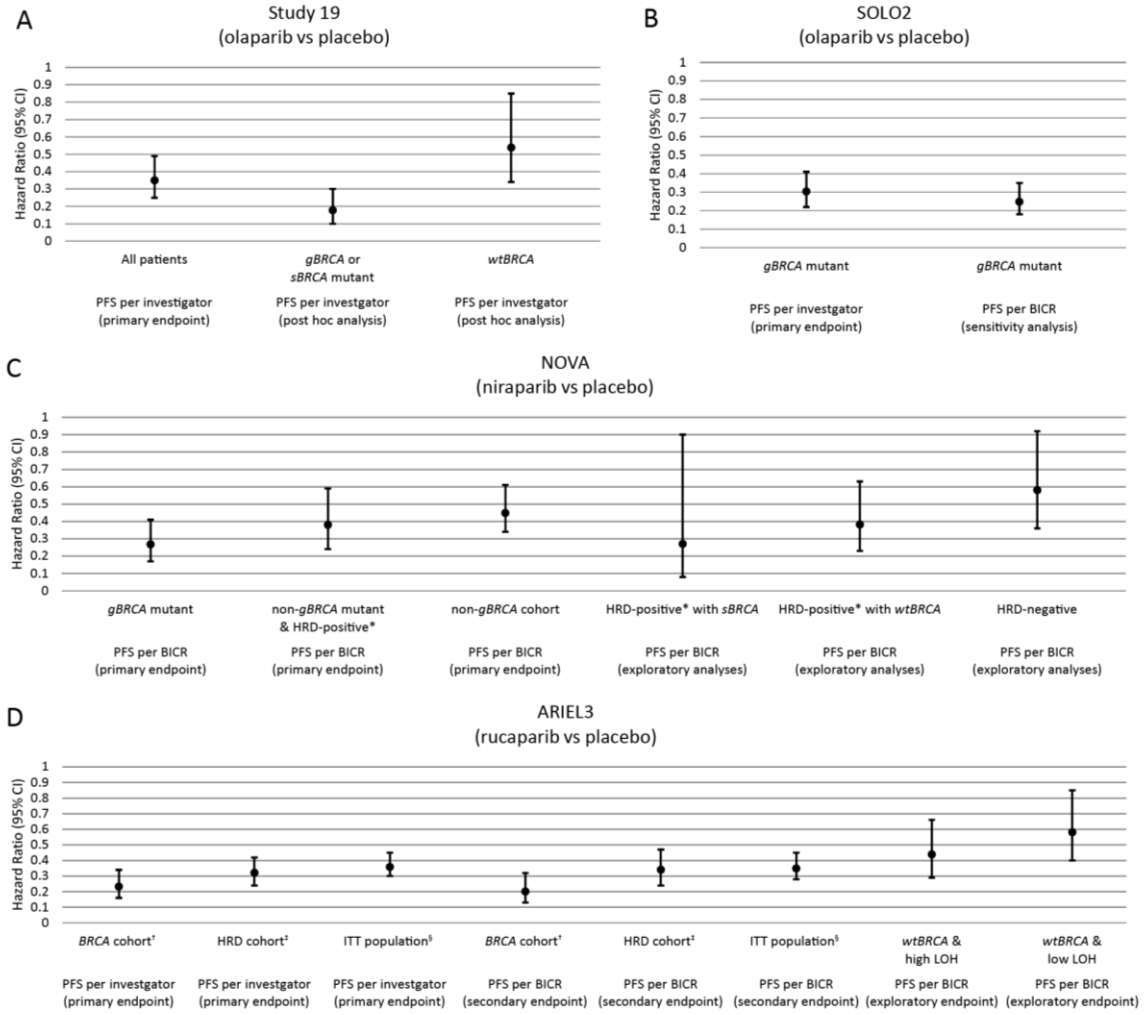
Figure 1. Estimated prevalence and incidence of ovarian cancer in the US from 2001 to 2015.



US: United States.

Source: National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER) Cancer Statistics Review (CSR) 1975-2015 – Ovary Section and archival CSRs from 2001 to 2014[2,4] Original plot – copyright permission not needed **All figures to be redrawn to consistent journal style**

Figure 2. Hazard ratios of progression-free survival (assessed by different methods) in four key clinical trials evaluating PARP inhibitors as maintenance therapy for recurrent ovarian carcinoma in differing patient populations

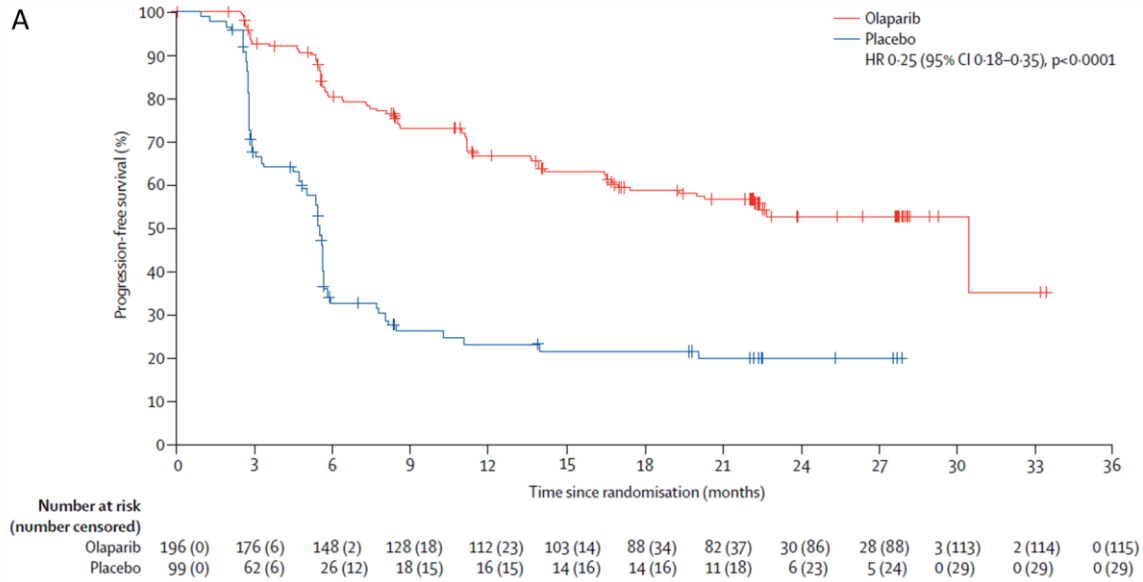


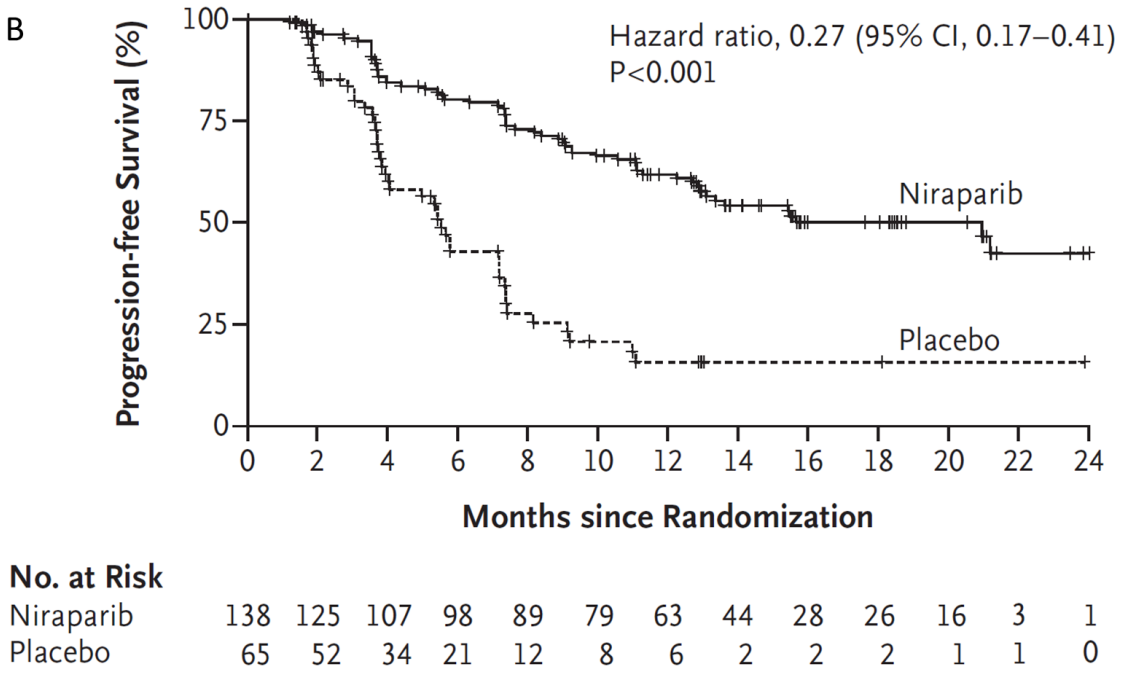
Note that PFS was assessed using different methods in the four studies: SOLO2, Study 19 and ARIEL3 were investigator assessed, whereas NOVA was BICR assessed. The populations in these studies had different mutation profiles and inclusion/exclusion criteria, so the results are not directly comparable.

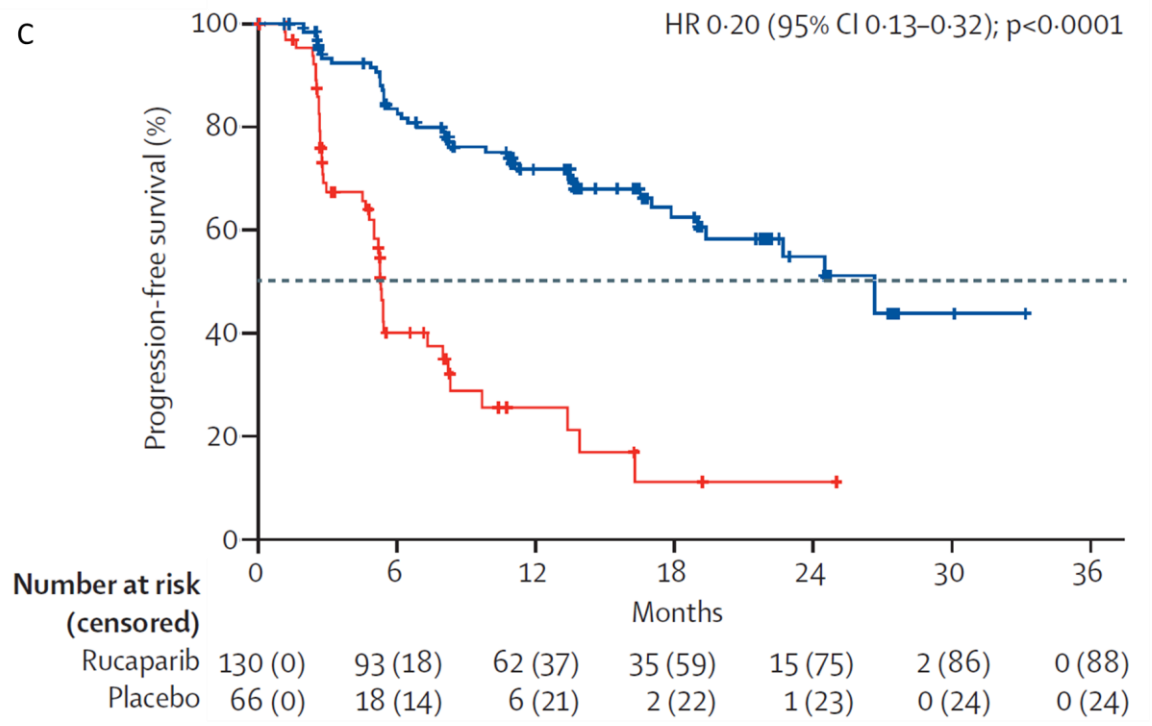
*HRD-positive was defined as having HRD according to the myChoice HRD test (Myriad Genetics). †Includes patients with a *gBRCA* or *sBRCA* mutation. ‡Includes patients with a *gBRCA* or *sBRCA* mutation and patients with *wtBRCA* and high LOH defined as ≥16% genomic LOH per T5 NGS assay (Foundation Medicine, Cambridge, MA, USA). §Includes all patients enrolled (*gBRCA* mutant, *sBRCA* mutant, *wtBRCA* and high LOH, *wtBRCA* and low LOH, *wtBRCA* and LOH indeterminate). BICR, blinded independent central review; *BRCA*: breast cancer gene; *gBRCA*: germline *BRCA1* or *BRCA2*; CI: confidence interval; HRD: homologous recombination deficiency; ITT: intent to treat; LOH: loss of heterozygosity; NGS: next-generation sequencing; s*BRCA*: somatic *BRCA1* or *BRCA2*; *wtBRCA*, wild-type *BRCA1* or *BRCA2*.

Source: Plotted from data presented in Pujade-Lauraine et al., 2017[15], Ledermann et al., 2012,[13] Mirza et al., 2016[10] and Coleman et al., 2017[11] Copyright permission not needed

Figure 3. Kaplan-Meier plots of BICR-assessed progression-free survival in patients with *BRCA*1/2 mutations in A. the SOLO2 (sensitivity analysis), B. the NOVA (primary endpoint) and C. the ARIEL3 (secondary endpoint) trials during maintenance treatment of recurrent ovarian carcinoma





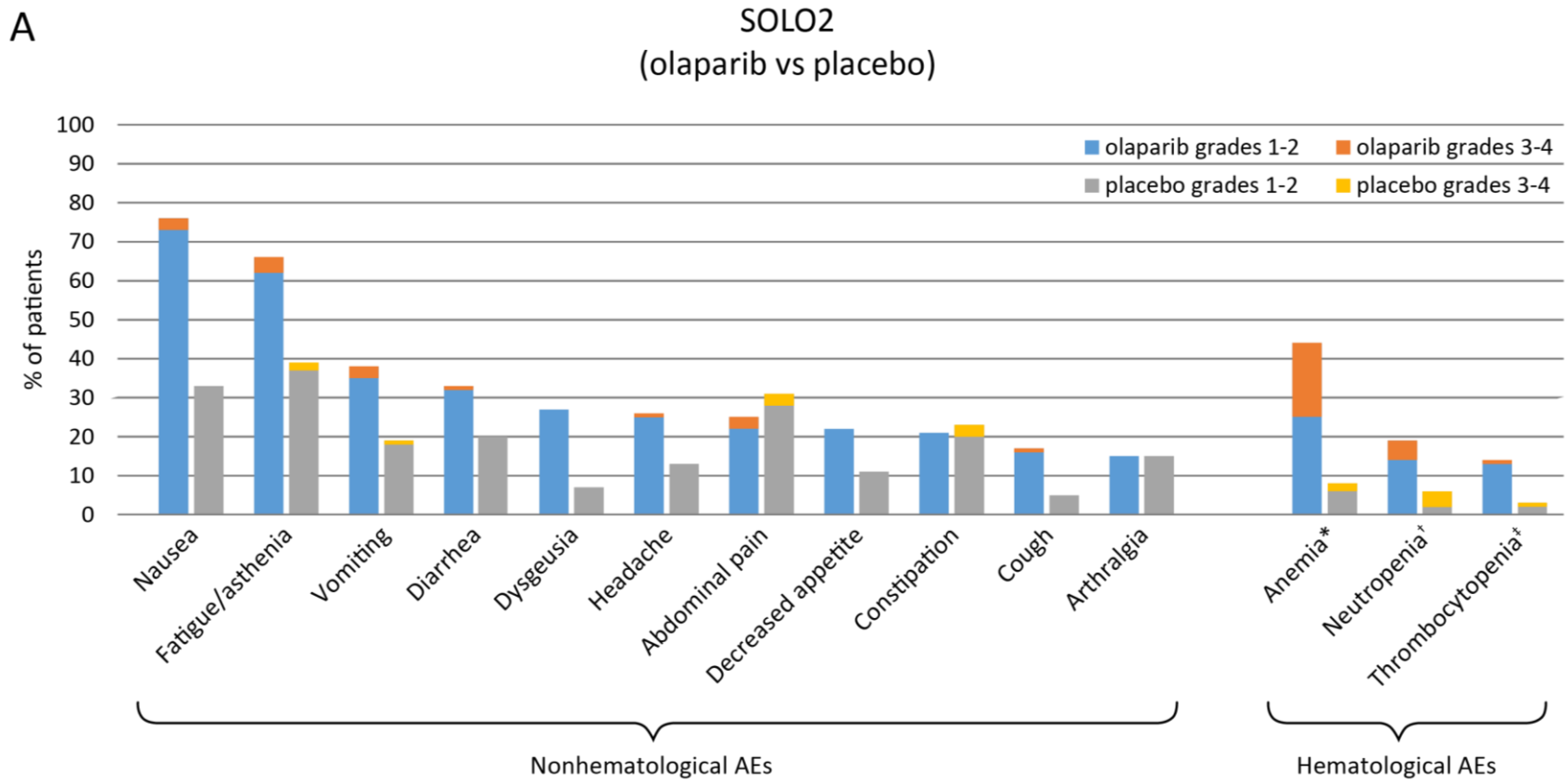


The data shown in panels A (from SOLO2) and B (from NOVA) include patients with germline *BRCA* mutations only (no somatic BRCA mutations), while the data shown in panel C from ARIEL3 includes both somatic and germline *BRCA* mutations.

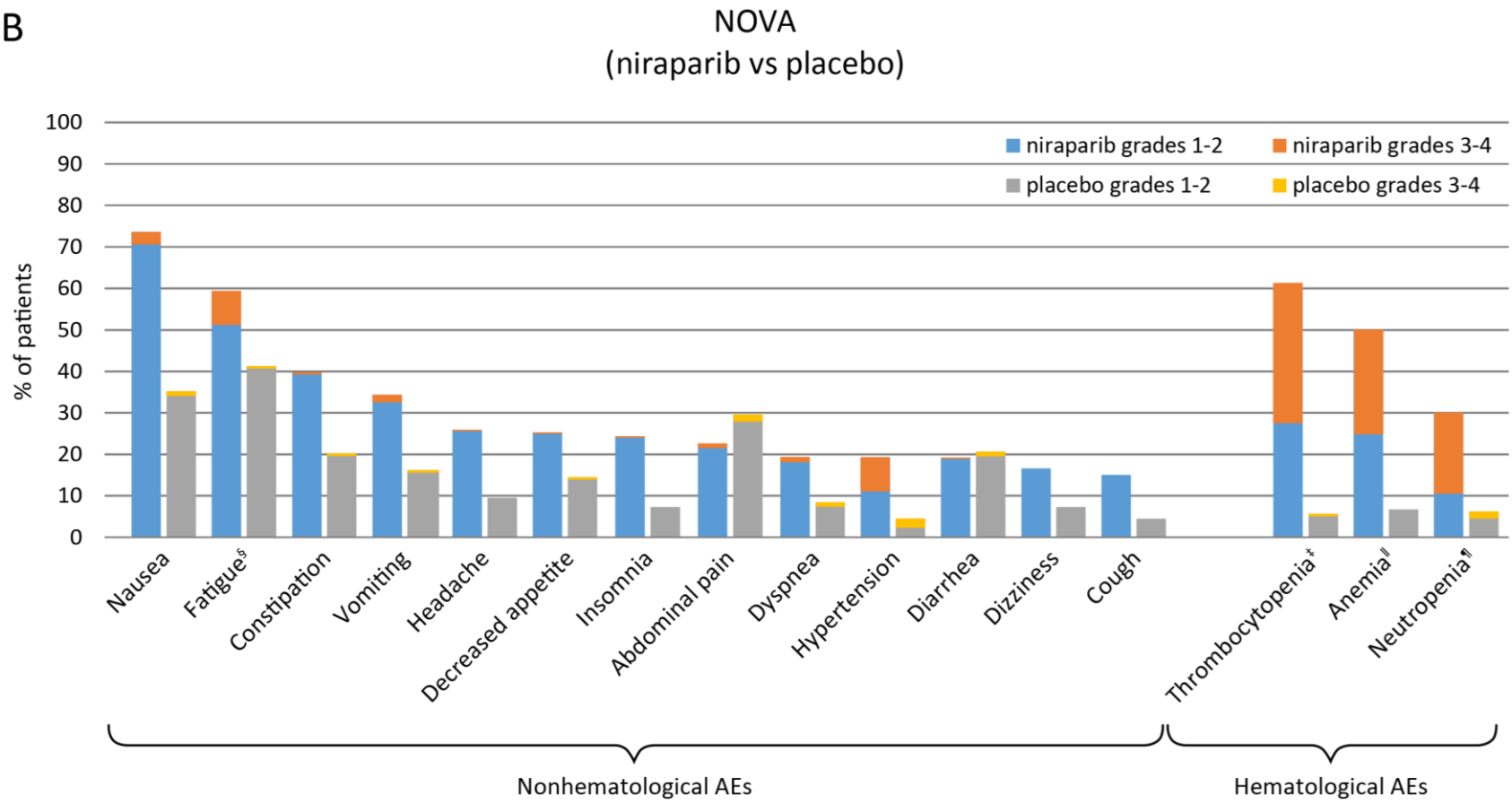
BICR: blinded independent central review; CI, confidence interval; HR: hazard ratio.

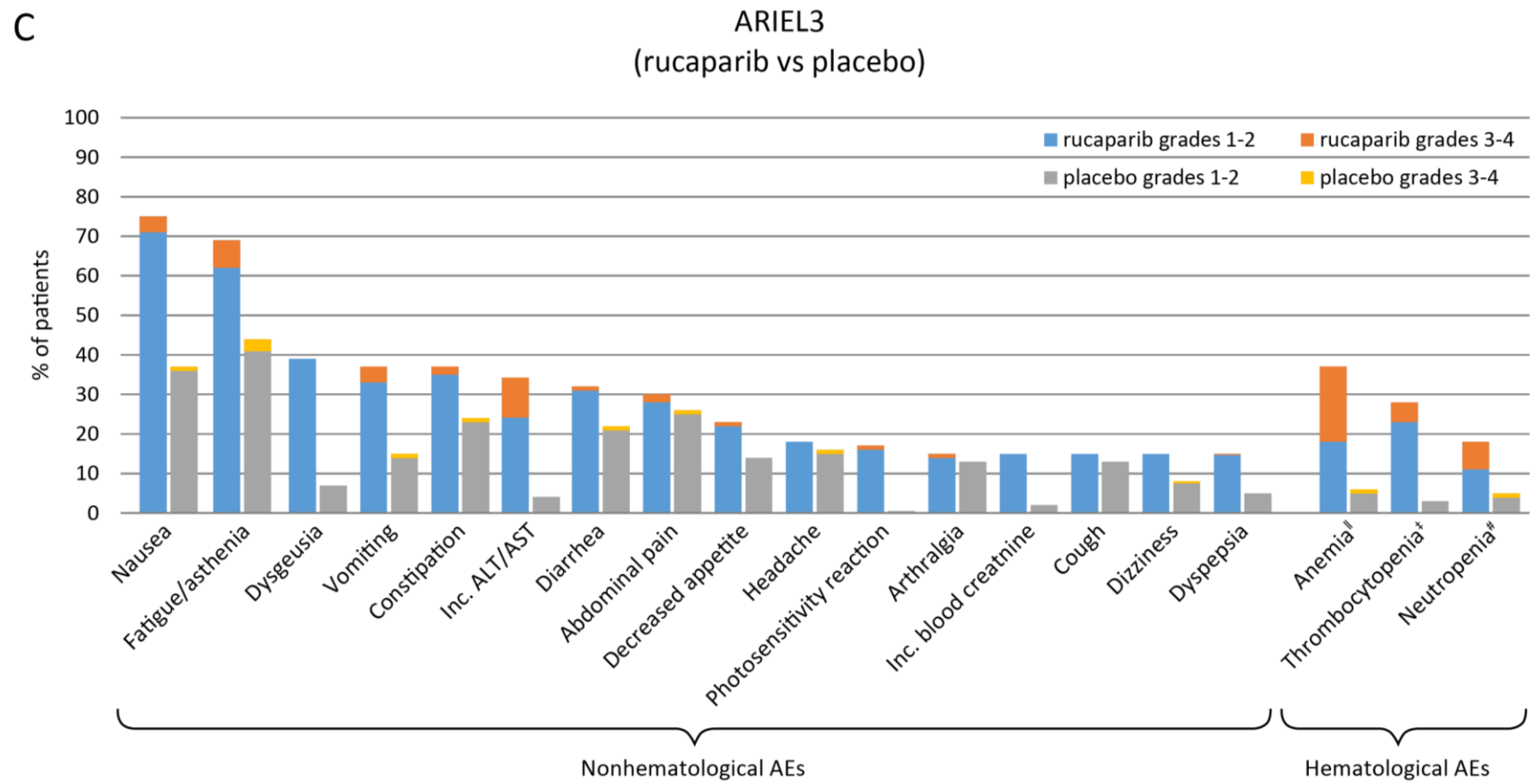
Source: Coleman et al., 2017,[11] Pujade-Lauraine et al., 2017[15] and Mirza et al., 2016[10] Copyright permissions to be obtained

Figure 4. Most frequent (≥15% patients in the treatment arm) non-haematological and haematological adverse events reported in the A. SOLO2, B. NOVA and C. ARIEL3 trials during maintenance treatment of recurrent ovarian carcinoma



B


NOVA
(niraparib vs placebo)
niraparib grades 1-2
niraparib grades 3-4
placebo grades 1-2
placebo grades 3-4
% of patients
100
90
80
70
60
50
40
30
20
10
0
Nausea
Fatigue§
Constipation
Vomiting
Headache
Decreased appetite
Insomnia
Abdominal pain
Dyspnea
Hypertension
Diarrhea
Dizziness
Cough
Thrombocytopenia‡
Anemia‖
Neutropenia¶
Nonhematological AEs
Hematological AEs



Note that the populations in these studies had differing mutation profiles and inclusion/exclusion criteria differed so the findings are not directly comparable. *Includes anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased. †Includes neutropenia, febrile neutropenia, neutropenic sepsis, neutrophil count decreased, granulocytopenia, and granulocyte count decreased. ‡Includes thrombocytopenia and

platelet count decreased. [§]Includes fatigue, asthenia, malaise, and lethargy. [‖]Includes anaemia and decreased haemoglobin count. [¶]Includes neutropenia, decreased neutrophil count, and febrile neutropenia. [#]Includes neutropenia and decreased neutrophil count. ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Source: Plotted from data in Pujade-Lauraine et al., 2017[15], Mirza et al., 2016[10] and Coleman et al., 2017[11] – Copyright permission not needed