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Review Article

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Insights into ovarian cancer care: report from the ANZGOG Ovarian Cancer Webinar Series 2020

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ABSTRACT

Epithelial ovarian cancer (EOC) is among the top ten causes of cancer deaths worldwide, and is one of the most lethal gynecological malignancies in high income countries, with incidence and death rates expected to rise particularly in Asian countries where ovarian cancer is among the 5 most common cancers. Despite the plethora of randomised clinical trials investigating various systemic treatment options in EOC over the last few decades, both progression-free and overall survival have remained at approximately 16 and 40 months respectively. To date the greatest impact on treatment has been made by the use of poly (ADP-ribose) polymerase (PARP) inhibitors in women with advanced EOC and a *BRCA1/2* mutation. Inhibition of PARP, the key enzyme in base excision repair, is based on synthetic lethality whereby alternative DNA repair pathways in tumor cells that are deficient in homologous recombination is blocked, rendering them unviable and leading to cell death. The Australia New Zealand Gynaecological Oncology Group (ANZGOG) is the national gynecological cancer clinical trials organization for Australia and New Zealand. ANZGOG's purpose is to improve outcomes and quality of life for women with gynecological cancer through cooperative clinical trials and undertaking multidisciplinary research into the causes, prevention and treatments of gynecological cancer. This review summarizes current ovarian

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Andreas Obermair, Tarek Meniawy and Paul Cohen received honoraria from Astrazeneca relevant to the webinar series (Paul Cohen donated support to ANZGOG). The authors declare no conflict of interest relevant to the current manuscript.

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cancer research and treatment approaches presented by Australian and New Zealand experts in the field at the 2020 ANZGOG webinar series entitled “Ovarian Cancer systems of Care”.

Keywords: Ovarian Cancer; PARP Inhibitors; High-Grade Serous Ovarian Cancer; Neoadjuvant Chemotherapy; Homologous Recombination Deficiency; *BRCA1/2* Mutation

INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for more than 313,000 new cancer cases and 207,000 deaths annually, and remains the most lethal gynecological malignancy in high income countries, with cancer deaths expected to triple by 2050 predominantly due to rising life expectancy [1,2]. Despite improvements in the EOC treatment paradigm and survival over the past four decades, the 5-year survival rates remains under 50% and varies according to tumor subtype, with tubo-ovarian high-grade serous carcinomas having the worst prognosis [3,4]. Poor survival rates have largely been due to ineffective disease screening options, peritoneal dissemination at the time of diagnosis, intrinsic and acquired drug resistance [5]. This review summarizes the latest developments in ovarian cancer diagnosis, genetic testing, chemotherapy and surgical interventions, and follow-up presented at the 2020 Australia New Zealand Gynaecological Oncology Group (ANZGOG) Ovarian Cancer Systems of Care webinar series. A major focus of the webinar series was treatment of the most fatal and frequent ovarian cancer subtypes. Treatment of the relatively rare subtypes, including low-grade serous, clear cell and mucinous and other non-epithelial carcinoma, for which there may be fertility sparing treatment options, was not within the scope of this webinar series, and has been recently reviewed elsewhere [6].

DNA REPAIR DEFECTIVE OVARIAN CANCER: IMPLICATIONS FOR THERAPY

The identification of *BRCA1/2* as ovarian cancer predisposition genes over 25 years ago, and elucidation of their role in DNA damage repair, has led to significant changes in treatment approaches in the past 5–10 years [7,8]. High-grade serous tubo-ovarian carcinomas (HGSOC), accounts for approximately 70% of ovarian cancer deaths, and are characterized by a high level of genomic instability and ubiquitous *TP53* mutations [9]. Approximately half of HGSOCs are defective in homologous recombination (HR) repair pathways, which arise predominantly from mutation events in *BRCA1/2*. HR deficiency in tumors is a key factor in platinum-sensitive HGSOCs, and provides a rationale for targeted treatment with poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis) [10]. Farmer and colleagues first showed that *BRCA1* or *BRCA2* dysfunction can sensitize cells to inhibition of PARP activity [11]. The recognition of *BRCA1/2* mutations as a predictive biomarker for response to PARPi therapy and the activity of olaparib, a PARPi specifically in ovarian cancer, was first demonstrated in the landmark proof-of-concept trial reporting an objective response rate of 33% (95% confidence interval [CI]=20%–51%) in women with recurrent ovarian cancer carrying germline *BRCA1/2* mutations [12]. Subsequent subanalyses of platinum-sensitive HGSOC patients from Study 19 (NCT00753545) [13] also reported significantly longer progression-free survival (PFS) associated with olaparib as maintenance therapy compared to placebo, and was more prominent in women with *BRCA1/2* mutations (median PFS, 7.4 vs 5.5 months; p=0.007) [14].

Similar benefit of PARPi therapy was also demonstrated in frontline maintenance therapy following response to platinum-based chemotherapy in patients with advanced EOC and *BRCA1/2* mutations. The SOLO1 trial (NCT01844986) investigated olaparib as maintenance therapy in this population and reported a 70% lower risk of disease progression or death compared to placebo (hazard ratio=0.30; 95% CI=0.23–0.41; p<0.001) [15]. Approximately half of women with a *BRCA1/2* mutation treated with olaparib for only 2 years remained disease-free up to 5 years, with a median disease-free survival of 56.0 vs. 13.8 months, which for the first time suggests the possibility of changing the natural history of ovarian cancer with first-line treatment [15]. This is unprecedented particularly for HGSOC tumors that are known as the silent killers, and it is likely that women with other HR deficiencies will similarly benefit from olaparib treatment.

The ARIEL2 study (NCT01891344) was specifically designed to assess the PARPi rucaparib beyond *BRCA1/2* mutation status in high-grade advanced platinum-sensitive tumors [16]. Women were classified according to loss of heterozygosity (LOH) in their tumors, using methods developed by Wang and colleagues [17], into three HR deficiency subgroups: *BRCA* mutant (deleterious germline or somatic), *BRCA1/2* wild-type and high level of LOH, or *BRCA1/2* wild-type and low LOH. Women with *BRCA1/2* mutations and high LOH or *BRCA1/2* wild-type and high LOH tumors treated with oral rucaparib had longer PFS compared to those with *BRCA1/2* wild-type and low LOH tumors (12.8 vs 5.7 vs 5.2 months) [16]. These results highlighted a mechanism for PARPi resistance, and suggest that mutation and methylation status of other HR-related genes, such as *RAD51C*, *RAD51D* and *PALB2*, may be associated with high genomic LOH and potentially with response to PARPi. Kondrashova and colleagues [18] used patient-derived xenograft models, which retain major genetic characteristics seen in the original tumor, from rucaparib-resistant ARIEL2 patients and showed that primary mutations in *RAD51C* and *RAD51D* impaired HR function leading to sensitivity to rucaparib, and that secondary mutations in these genes reinstated HR function and were the mechanism through which resistance to PARPi was acquired.

Genomic analysis of HGSOC tumors has shown that 20% of HGSOC tumors have germline or somatic *BRCA1/2* mutations, and 11% have lost *BRCA1* expression through DNA hypermethylation which causes epigenetic silencing [9]. Additionally, overall survival (OS) in patients with epigenetically silenced *BRCA1* was similar to *BRCA1* wild-type patients, but worse than *BRCA1* mutant patients [9]. An association between hypermethylation and patient survival has not been confirmed to date, and reports of an association between methylation and survival in women treated with PARPi have been conflicting [16,19]. Patient-derived xenograft models as well as 21 *BRCA1*-methylated HGSOC patient samples from the ARIEL2 trial confirmed that homozygous *BRCA1* methylation predicts PARPi response, whereas hemizygous *BRCA1* methylation does not, highlighting for the first time that *BRCA1* methylation can be used to predict PARPi response pre-treatment, that methylation zygosity was conceptually similar to mutation zygosity for *BRCA1*, and that *BRCA1* methylation loss can occur after exposure to chemotherapy [20]. Further validation in a larger patient sample is required to confirm these findings, particularly in an early treatment setting.

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UPFRONT SURGERY VERSUS NEOADJUVANT CHEMOTHERAPY: BRAWN VERSUS BIOLOGY

Treatment of women with suspected EOC involves initial investigations and examinations using imaging and CA-125. Women with early stage disease (20%–30%) may be successfully treated with primary debulking surgery (PDS) followed by adjuvant chemotherapy. However, for advanced stage tumors, which accounts for 70%–80% of cases, complete or optimal cytoreduction (no visible or <1 cm residual disease; R0) may not be possible, and the usual treatment approach is neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and adjuvant chemotherapy.

The landmark study of PDS to treat stage II and III EOC over four decades ago demonstrated that the survival benefit was inversely proportional to the size of residual disease up to 1.5 cm, with poor survival (12.7 months) associated with residual disease ≥1.5 cm irrespective of the volume of the tumor [21]. Retrospective studies have widely reported that PDS to the level of no macroscopic residual disease (R0) is necessary for optimal OS and PFS in advanced EOC [22,23]. A meta-analysis of 18 studies and over 13,000 advanced EOC patients showed that even a modest rate of 25% of patients undergoing complete resection had a median survival of approximately 45 months [24]. These findings led to the acceptance of treatment regimens that included PDS to R0 levels, including radical debulking surgery of extensive disease involving the liver, spleen, diaphragm, or epicardial nodes. The subsequent rise in perioperative morbidity and mortality has limited treatment options for women with significant comorbidities. Falconer and colleagues evaluated survival outcomes in a population-based cohort study following a structured shift from conventional debulking surgery to ultra-radical surgery, defined as surgery beyond the traditional anatomical boundaries in order to achieve complete resection, and found no improvement in survival in women with advanced EOC, despite higher rates of complete resection [25].

Given the limitations and challenges of complete resection, there has been considerable focus on NACT as an alternative to PDS. A systematic review of two randomised controlled trials (RCTs) [26,27] and 22 observational studies published between 1998 and 2016 reported that NACT-IDS improved perioperative outcomes and optimal debulking rates, but there was no improvement in OS compared to PDS [28]. Historically women who were elderly with large tumor burdens were treated with NACT-IDS, which may partially explain this result. A retrospective study of data from the National Cancer Database, consisting of up to 9,800 advanced EOC patients treated with NACT-IDS versus up to 27,000 patients who underwent PDS suggested worse OS in the NACT-IDS group [29]. However, data from 2 RCTs of women with biopsy-proven stage IIIC and IV invasive EOC comparing PDS and chemotherapy with NACT-IDS and adjuvant chemotherapy showed that survival in the NACT-IDS group was similar or better than the PDS group [30], suggesting cautious use of retrospective studies as evidence in favour of upfront PDS.

The Society of Gynecologic Oncology and the American Society of Clinical Oncology recommend that PDS ideally to the level of R0 is the preferred treatment approach for women with stage IIIC or IV invasive EOC [31]. PDS is not recommended by the European Society of Gynaecological Oncology (ESGO) if there is diffuse deep infiltration of the root of the small bowel mesentery, diffuse carcinomatosis of the small bowel such that resection would lead to a short bowel syndrome (remaining bowel <1.5 m), or if there is diffuse involvement or deep infiltration of other organs such as the stomach or duodenum, head or middle part of the

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pancreas. PDS is also not advised if there is spread to other sites e.g., coeliac trunk, hepatic arteries, left gastric artery, or other visceral metastasis e.g., lung, liver, bone or brain [32]. A 2020 update of the ESGO quality indicators for stage III and IV EOC included an optimal target rate of >65% R0 with either PDS or NACT-IDS, >50% PDS, and that women who can undergo PDS with a 'reasonable complication rate' benefit most from PDS [33]. These guidelines have not been revised despite mounting evidence from RCTs that compared to PDS, NACT-IDS was non-inferior for PFS or OS, and there was significantly less morbidity and mortality.

The earliest non-inferiority trials of PDS versus NACT-IDS showed that tumor debulking to R0 was the most important indicator of OS, and rates were higher in the NACT-IDS treatment arms [26,27,34,35]. The EORTC (NCT00003636) and CHORUS (NCT00075712) trials highlighted higher rates of perioperative mortality associated with PDS compared to NACT-IDS (2.5% vs. 0.7% [EORTC], and 6% vs. 0.5% [CHORUS]) [26,27]. The rates of R0 in both trials were also lower in the PDS arms compared to the NACT-IDS arms (18% vs. 45% [EORTC], and 17% vs. 39% [CHORUS]). In the SCORPION (NCT01461850) and JCOG0602 (ACTRN12618000109202) trials, higher rates of R0 were achieved in the PDS arms (46% and 12% respectively), and PFS and OS for both trials were comparable and non-inferior for NACT-IDS. However, the postoperative event rates were higher in the PDS arms of both trials, and the perioperative death rate associated with PDS was unsustainably high (7/84, 8%) compared to NACT-IDS (none) in the SCORPION trial [34,35]. Coleridge and colleagues confirmed the non-inferiority of NACT-IDS compared to PDS in a meta-analysis of these four RCTs comparing NACT-IDS and PDS followed by chemotherapy, and found no significant difference in PFS or OS according to treatment approach ($p \geq 0.400$). This analysis highlighted significantly higher risks of grade 3 adverse events including venous thromboembolism, blood transfusions, and infections, as well as 30-day postoperative mortality in women receiving PDS compared to NACT-IDS [36].

Current rates of NACT use prior to surgery have more than doubled among certified gynecological oncology practices in Australia and New Zealand since 2007 (43% vs. 16%) [37]. This increase is driven by the surgeon's definition of optimal debulking being R0, medical comorbidities (87%), patient age (68%) and disease-related characteristics such as involvement of the base of mesentery (94%), large volume of peritoneal disease (53%) or parenchymal liver metastases (40%) [37]. NACT should be considered in women with advanced disease to reduce the tumor bulk and increase the likelihood of complete resection during IDS. NACT-IDS has also been shown to be more cost-effective than PDS given that the latter generally involves more complex surgery [38].

The challenges and debate over NACT-IDS have continued, fuelled by differences in interpretation of these studies that have led to variable surgical practices worldwide, and calls for standardization of treatment approaches [39]. The Trial on Radical Upfront Surgery in Advanced Ovarian Cancer (TRUST) is an international multi-center RCT that aims to investigate the hypothesis that PDS is superior to NACT-IDS for OS in advanced EOC [40]. Stringent quality assurance criteria are required for participation, including a minimum of 50% complete resection rate in upfront surgery for stage IIIB–IVB patients, over 36 debulking surgeries per year, and consent to a review of 24 surgeries and pathology reports from the previous year. Additionally, surgeons must believe that resection to R0 level is likely with PDS. Completion of follow-up for the primary endpoint of OS is expected in 2024. The trial also includes various other secondary endpoints such as PFS and quality of life measures, as

well as exploratory endpoints such as timing of tissue collection and blood samples that will facilitate translational research.

Various factors may influence the timing of surgery following NACT, as has recently been seen during the COVID-19 pandemic, where restrictions imposed on healthcare facilities led to delays in interval surgeries and extensions on NACT cycles. Recent studies of survival outcomes and delayed debulking surgery following NACT concluded that delays between NACT and IDS were not associated with worse OS after adjusting for known confounders. However, debulking surgery was necessary in order to maintain improved survival with the caveat that it was undertaken after at least three cycles of NACT [41,42].

As treatment regimens have evolved over the past two decades, there is evidence that the 5-year OS has improved. An Australian population-based retrospective review of stage III and IV EOC patients treated between 1982 and 2013 showed rising rates of utilisation of NACT-IDS (up to 40%–50% of HGSOC) in the previous two decades, and that this was associated with improvements in cytoreduction to R0 levels (62%) and 5-year survival (45%) [43]. The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) was shown to improve outcomes in stage III EOC patients receiving NACT-IDS, with no increase in side effects, compared to surgery alone [44]. It is worth noting that although both patient groups in this study achieved high rates of complete cytoreduction (69% and 67%), the median OS was relatively low (45.7 and 33.9 months) compared to other less highly selected patient populations. Two similar studies in Korean [45] and Chinese women [46] found preliminary evidence of improved OS in women treated with HIPEC and NACT-IDS compared to IDS only. Additional follow-up would be necessary to confirm the role for HIPEC in longer-term OS and possibly PFS.

ASSESSMENT OF TUMOR RESPONSE: WHY? WHAT? HOW? AND WHEN?

Battling chemoresistance to try to improve patient outcomes, and balancing issues of surgical complications, including futile laparotomies, complications due to delayed chemotherapy, hospital costs, and the personal impact on the patient, remains a dilemma. Given the evidence from clinical trials for non-inferior survival in women treated with of NACT compared to PDS, higher rates of optimal debulking, and lower rates of major postoperative complications, NACT provides an opportunity for reduction of disease burden in women with advanced EOC, as well as time for patient recovery.

Once NACT has commenced, there is significant heterogeneity in selection of who and when women should undergo IDS. While the current convention is IDS after 3 cycles of NACT, in the recent ICON8 trial (NCT01654146) 80% of women had interval surgery after 1–3 cycles and 21% after 4–6 cycles [47]. This raises questions as to what criteria was used to decide if or when patients should have surgery. In the absence of a direct marker, the only objective criteria currently available for assessing patient fitness for interval surgery and disease resectability are CA-125, computed tomography (CT) scans, or laparoscopy. However, there are other subjective influences that enable decision-making, e.g., women with poor prognosis, older more frail women with comorbidities, greater disease burden, patient wishes, financial constraints, surgeon's opinion, and operative time. In the ICON8 trial that compared two dose-dense weekly regimens to standard 3-weekly chemotherapy, 14% of

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the 779 women randomised to NACT and delayed primary surgery had no surgery, and for another 9% it was unknown whether surgery was performed [47].

The Gynaecological Cancer Intergroup (GCIG) criteria for assessing patient response to chemotherapy are based on data from clinical trials using CA-125. Women considered to have stable disease is based on CA-125 that is not progressing or showing evidence of a partial response, target lesions that are shown to be stable in CT scans, and no new lesions [48]. There is a paucity of evidence for using CA-125 and CT scans in NACT. A small trial of 103 women with stage IIIC and IV EOC evaluated whether changes in the absolute levels of CA-125 could predict the rate of optimal debulking in women undergoing NACT-IDS. While 96% of women were optimally debulked (≤1 cm residual disease), the most significant predictive criteria was lower than average CA-125 (≤100 U/mL) preoperatively after three cycles of NACT. Additionally, this study showed that the preoperative level of CA-125 had no bearing on platinum resistant disease; only ≥3 cycles of NACT was predictive of platinum-resistance disease [49]. Kessous and colleagues [50] evaluated CA-125 levels and survival in 105 women with advanced EOC following NACT and found preliminary evidence to suggest that CA-125 was predictive of both long-term survival and successful debulking surgery after three cycles of NACT.

Laparoscopy may allow greater precision in identifying women who are likely to have successful IDS following NACT. Fagotti and colleagues [51] compared Response Evaluation Criteria in Solid Tumors (RECIST) criteria with GCIG criteria in conjunction with laparoscopy, and found that with the addition of laparoscopy to RECIST or GCIG criteria, the rate of explorative laparotomy dropped from 30% to 10% and 13% respectively. Bregar and colleagues [52] compared a scoring system using clinical and radiologic criteria with RECIST criteria to evaluate changes in tumor burden after initiation of NACT and before IDS. The surgical score was more predictive of successful optimal debulking compared to RECIST alone, but neither the scoring system nor RECIST criteria correlated with PFS or OS [52]. Bohm and colleagues [53] developed a histopathologic chemotherapy response score (CRS), which stratifies women into complete/near complete (CRS1), partial (CRS2), or no/minimal (CRS3) response [53]. This system had a high level or reproducibility and was predictive of residual disease in women with HGSOC undergoing NACT-IDS. Cohen and colleagues showed in a recent meta-analysis of 809 women with stage IIIC/IV HGSOC that CA-125 levels pre-IDS did not reliably predict survival or residual disease status following NACT. CRS3 scores were associated with PFS and OS, were predictive of *BRCA1/2* mutation status and platinum resistance, and was a reproducible biomarker that could be used to estimate the probability of early or late relapse [54]. A recent pilot study of the cancer cell proliferation marker Ki67 targeted in diffusion kurtosis magnetic resonance imaging has also shown promise as marker of response to NACT, but requires further evaluation [55].

There are also questions around when to assess response to chemotherapy. A study of positron emission tomography involving sequential F-18-fluorodeoxyglucose, a marker of metabolic activity, showed evidence that patient survival after NACT could be predicted as early as after the first cycle of NACT, and was more accurate than CA-125 changes or other clinical or histopathologic criteria [56]. Torres and colleagues examined the correlation between OS and molecular subtype and intraperitoneal disease dissemination patterns in women with HGSOC undergoing PDS, and reported significantly shorter median OS in women with mesenchymal versus non-mesenchymal subtypes (34.2 vs. 44.6 months). Mesenchymal subtypes are associated with more frequent upper abdominal or military disease, which may account for the lower rates of complete resection seen in this group compared to non-mesenchymal subtypes

(11% vs. 27%) [57]. Analysis of a range of other known prognostic factors in multivariable models reinforced the 'gold standard' of complete resection as an independent predictor of OS in women with HGSOC irrespective of molecular subtype.

SYSTEMIC TREATMENT FOR OVARIAN CANCER

The current standard of care for women with advanced EOC in Australia is carboplatin (area under the curve [AUC], 5–6) and paclitaxel (175 mg/m^2) given every 3 weeks for a total of 6 cycles. Women with stage III and all stage IV disease who are suboptimal debulked can be offered bevacizumab (7.5 mg/kg) given every three weeks in combination with chemotherapy and as maintenance therapy for up to a total of 18 doses. Women with germline or somatic *BRCA1/2* mutations are prescribed maintenance therapy of olaparib (300 mg twice daily) for 2 years [58].

Other variations of carboplatin and paclitaxel for ovarian cancer include the dose-dense protocol (carboplatin AUC 5–6 every 3 weeks, in combination with weekly paclitaxel 80 mg/m^2) offered in Japanese or Asian populations, and the elderly and frail population may receive carboplatin (AUC 2) and paclitaxel (60 mg/m^2) every week for 3 of a 4-week cycle [47,59]. The dose-dense regimen has been evaluated in several trials (**Table 1**) [47,60-62]. The JGOG3016 trial showed that weekly paclitaxel and three-weekly carboplatin was superior to three-weekly carboplatin and paclitaxel in a Japanese population of women with epithelial, fallopian tube and primary peritoneal tumors [60]. Dose-dense therapy was associated with longer PFS (28.2 vs. 17.5 months), and more importantly, a clinically significant increase in the median OS (100.5 vs. 62.2 months). However, this survival advantage appears to apply specifically to the Japanese population, as similar trials performed elsewhere (ICON8, MITO7, GOG262), did not show similar results (**Table 1**) [47,60-62]. The ICON8 trial evaluated three regimens including standard of care carboplatin and paclitaxel, dose-dense protocol (AUC 5/6 every 3 weeks; 80 mg/m^2 weekly) and weekly protocol (AUC 2 and 80 mg/m^2 weekly). Women enrolled in ICON8 were predominantly Caucasian and the median survival were similar in all three groups for both PFS (17.7 vs. 20.8 vs. 21.0 months) and OS (47.4 vs. 54.1 vs. 53.4 months) [47,61,62]. The recent EWOC-1 trial (NCT02001272) of elderly women with advanced disease using a geriatric vulnerability score, and showed that the combination of carboplatin and paclitaxel chemotherapy was significantly better in than the current standard of three-weekly single-agent carboplatin [59]. The median PFS for single agent carboplatin was 4.8 months, as compared to 12.5 months for standard carboplatin and paclitaxel (AUC 5/6; 175

Table 1. Changing dose intensity – dose dense therapy

Variables	JGOG3016	GOG262	ICON8	MITO-7
Reference	[60]	[61]	[47]	[62]
ClinicalTrials.gov ID	NCT00226915	NCT01167712	NCT01654146	NCT00660842
No. of patients	637	692	1,566	822
Tumor stage	II–IV	III–IV suboptimal	IC–IV	IC–IV
Treatment arm	• Paclitaxel 180 mg/m^2 + Carboplatin AUC 6, 3-weekly • Paclitaxel 80 mg/m^2 (D1, D8 & D15) + Carboplatin AUC 6, 3-weekly	• Paclitaxel 175 mg/m^2 + Carboplatin AUC 6, 3-weekly ± bevacizumab • Paclitaxel 80 mg/m^2 (D1, D8 & D15) + Carboplatin AUC 6, 3-weekly ± bevacizumab	• Paclitaxel 175 mg/m^2 + Carboplatin AUC 5, 3-weekly • Paclitaxel 80 mg/m^2 (D1, D8 & D15) + Carboplatin AUC 5, 3-weekly • Paclitaxel 80 mg/m^2 + Carboplatin AUC 2, weekly	• Paclitaxel 175 mg/m^2 + Carboplatin AUC 6, 3-weekly • Paclitaxel 60 mg/m^2 + Carboplatin AUC 2, weekly
Median PFS (mo)	28.2 vs. 17.5 (p=0.039)	14.0 vs. 14.7 (p=ns)	24.4 vs. 27.3 vs. 26.2 (p=ns)	17.3 vs. 18.3 (p=ns)
Median OS (mo)	100.5 vs. 62.2 (p=0.039)	39.0 vs. 40.2 (p=ns)	46.5 vs. 48.1 vs. 54.0 (p=ns)	2-yr OS: 78.9% vs. 77.3% (p=ns)

ns, not significant; OS, overall survival; PFS, progression-free survival.

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mg/m^2; both every 3 weeks) and 8.3 months for weekly carboplatin and paclitaxel (AUC 2 and 60 mg/m^2 both every week for 3 weeks out of a 4-week cycle) [59], highlighting the need to revisit treatment approaches in elderly women.

Adding other cytotoxic agents to carboplatin and paclitaxel did not provide additional benefit in PFS or OS, as evidenced by GOG182/ICON5 trial (NCT00011986). This trial evaluated 5 treatment regimens that incorporated gemcitabine, methoxypolyethylene glycosylated liposomal doxorubicin or topotecan compared to carboplatin and paclitaxel after debulking surgery [63]. Across the five treatment regimens, the median PFS and OS was 16 and 44 months respectively, and there were no improvements associated with any experimental regimen [63]. These estimates have remained consistent across almost all subsequent trials and analyses to date.

Changing the route of administration from intravenous to intraperitoneal have also been evaluated. The GOG104, GOG114, and GOG172 trials evaluated intravenous versus intraperitoneal administration for cisplatin-based chemotherapy, and found significant improvement in PFS associated with intraperitoneal administration [64-66]. The GOG172 in particular led to an alert by the National Cancer Institute and implementation and uptake of intraperitoneal therapy as part of the standard of care [67]. This was challenged by the GOG252 study, which convincingly showed no difference in PFS or OS associated with the route of chemotherapy administration [68] and questions whether there is a role of intraperitoneal chemotherapy.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor that is upregulated in EOC [69], has shown considerable success for frontline and maintenance therapy. The GOG218 and ICON7 trials, which added 15 and 7.5 mg/kg respectively to carboplatin and paclitaxel chemotherapy, showed modest improvements in PFS associated with the addition of bevacizumab [58,70]. However, in women at high risk of progression, as defined by stage III/IV disease with suboptimal debulking surgery, an improvement in PFS (16 vs. 10.5 months) and OS (39.7 vs. 30.2 months) was observed [71], leading to the approval of bevacizumab for stage IV and suboptimally debulked stage III disease in Australia.

There have been 3 trials in the maintenance setting in HGSOC that have been reported very recently, with only subtle differences between them with regard to patient population, type of PARPi drug used, and the timing of treatment that have consistently shown a significant improvement in PFS in women with *BRCA1/2* mutations or HR deficiency (**Table 2**) [72-74]. Analyses of over 47,000 patient records from the National Cancer Data Base highlight clinically significant disparities in the quality of treatment and OS and the need for consistency with treatment guidelines across all patient populations [75]. Beyond new drugs and trials for ovarian cancer, there are many issues that can be optimised to ensure the best patient outcomes, including surgical staging, attention to tumor biopsy collection to ensure correct pathological diagnosis and *BRCA1/2* testing (**Data S1**), stratifying women according to risk level, and access to clinical trials (**Table 3**).

TREATMENT OF RECURRENCE

Treatment of recurrent EOC remains a challenge primarily due to drug resistance, and patient outcome varies according to postoperative disease volume, response to platinum-

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Table 2. Maintenance trials in HGSOC

Variables	PRIMA	PAOLA	VELIA
ClinicalTrials.gov ID	NCT02655016	NCT02477644	NCT02470585
Reference	[72]	[73]	[74]
Patient population	· Stages III/IV HGSOC/endometrioid at high risk of recurrence · Stage III – residual disease · All NACT/IV eligible irrespective of residual disease · Must have CR/PR	· Stage IIIB-C, IV HGSOC · All patients regardless of residual disease/ NACT · Must have had at least 3 cycles of Bevacizumab pre-randomization · All NED or CR/PR	· Stage III/IV HGSOC · All patients regardless of residual disease/ NACT Upfront randomisation
HRD scoring	Myriad myCHOICE HRD HR score >42 or *BRCA1/2* mutation	Myriad myCHOICE HRD HR score >42 or *BRCA1/2* mutation	Myriad myCHOICE HRD HR score >33 or *BRCA1/2* mutation
First-line chemotherapy	>6 and <9 cycles of platinum-based chemotherapy; no Bevacizumab (not yet approved)	Platinum–taxane chemotherapy plus bevacizumab	6 cycles of carboplatin and paclitaxel; NACT permitted
Randomisation	2:1 Niraparib or placebo within 12 weeks of completion of last dose of chemotherapy	2:1 Olaparib or placebo ≥3 and <9 weeks after last dose of chemotherapy; Bevacizumab as maintenance	1:1:1 to control (chemotherapy + placebo); veliparib-combination-only; veliparib-throughout; ± maintenance in experimental arms
Duration	Niraparib 3 years	Bevacizumab 15 mg/kg for a total of 15 months; Olaparib 2 years	Veliparib (150 mg orally) throughout chemotherapy and maintenance 2 years
Primary endpoint	PFS by BICR; HRD>ITT	Investigator-assessed PFS in ITT population	Investigator-assessed PFS veliparib throughout vs. control-*BRCA*>HRD>ITT

BICR, blinded independent central review; CR, complete response; HGSOC, high grade serous ovarian cancer; HRD, homologous recombinant deficiency; ITT, intention to treat; Myriad myCHOICE, a laboratory test that detects HRD status; NACT, neoadjuvant chemotherapy; NED, no evidence of disease; PFS, progression-free survival; PR, partial response.

Table 3. Improving outcomes in ovarian cancer: what can we control?

Optimizing patient outcomes
· Surgical staging and debulking
· Ensuring correct pathological diagnosis
· Ensuring sufficient tumor tissue at biopsy and timely *BRCA1/2* testing (**Data S1**)
· Optimizing chemotherapy for dose and delivery
· Identify specific patients subsets for high/low surgical risk
· Patient access to clinical trials
· Optimal supportive care during and after chemotherapy
· Prophylactic risk-reducing bilateral salpingo-oophorectomy
· Selective about NACT
· Optimal management in recurrent settings
· Maintenance therapy with PARPi
· Bevacizumab in stage IV and suboptimally debulked stage III

NACT, neoadjuvant chemotherapy; PARPi, poly (ADP-ribose) polymerase inhibitor.

based chemotherapy, and genetic factors. **Table 4** summarizes the results of the randomised clinical trials focusing on recurrent ovarian cancer. The GOG0213 trial (NCT00565851) of the addition of bevacizumab to platinum-based chemotherapy after secondary surgical cytoreduction followed by maintenance therapy until progression, showed a marginally significant improvement in the median OS of women in this group compared to standard chemotherapy group (42.2 vs. 37.3 months) [76]. Secondary surgical cytoreduction may be performed safely in women with platinum-sensitive recurrent ovarian cancer, but there was no additional benefit to OS. It was also evident that subsequent chemotherapy was important for OS, but surgery was not required for all women with recurrent ovarian cancer [77].
The AURELIA trial (NCT00976911) demonstrated significant benefit with the addition of bevacizumab to single-agent chemotherapy for platinum-resistant disease [78]. Exploratory analysis of outcomes for primary platinum resistance (PPR) versus secondary platinum resistance (SPR) showed that PFS and OS benefit were more pronounced in women with SPR than PPR, and the addition of bevacizumab improved median OS from 15.6 months to

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Table 4. Recurrence trials

Variables	GOG-0213	AURELIA	SOLO/ENGOT-OV21 (ICON8)	ENGOT-OV16/NOVA	NSGO-AVANOVA2/ENGOT-ov24
Reference	[76]	[79]	[80]	[81]	[82]
ClinicalTrials.gov ID	NCT00565851	NCT00976911	NCT01874353	NCT01847274	NCT02354131
Patient population	674 women with a complete response to ≥3 cycles primary platinum CT; disease-free for at least 6 months from last CT treatment	361 women classified as PPR (73%) or SPR (27%)	294 women with ≥2 previous lines of platinum-based CT; in CR or PR to most recent CT regimen; platinum-sensitive disease; disease-free for at least 6 months from last platinum-based dose; predicted or suspected deleterious *BRCA1/2* mutation	553 women with/without germline *BRCA* (g*BRCA*) mutation; at least 2 platinum-based CT regimens; platinum-sensitive disease; CR or PR >6 months after last round of CT	97 women; ECOG 0–2, previous platinum-based first-line CT but ≤1 prior non-platinum-containing regimen for recurrent disease. Previous BEV or PARPis allowed
Tumor stage	All recurrent EOC	All platinum resistant	Relapsed histologically-confirmed high-grade EOC	Predominantly high-grade serous features; platinum-sensitivity	High-grade serous or endometrioid platinum-sensitive recurrent ovarian cancer
Randomisation	• Standard CT (6 cycles 3-weekly paclitaxel 175 mg/m^2 + carboplatin AUC 5) ± BEV, then BEV as maintenance every 3 weeks until progression or toxicity • Standard CT ± BEV ± prior secondary cytoreductive surgery	Single-agent CT weekly (paclitaxel or pegylated liposomal doxorubicin or Topotecan) for 4 weeks, then CT ± BEV every 2 weeks	2:1 Olaparib maintenance therapy or placebo	2:1 niraparib vs. placebo (138:65 niraparib:placebo in g*BRCA* cohort, and 234:116 niraparib:placebo in non-g*BRCA* cohort	1:1 stratified by HRD status to daily niraparib ± BEV every 3 weeks until disease progression
Median PFS (mo)	13.8 (13.0–14.7) in the CT + BEV group vs. 10.4 (9.7–11.0) in the CT only group; p<0.0001	PPR: 5.6 (CT + BEV) vs. 2.8 (CT alone) p<0.001; SPR: 10.2 (CT + BEV) vs. 3.7 (CT alone) p<0.001	19.4 vs. 5.5; p<0.0001 (BICR review 30.2 vs. 5.5; p<0.0001)	21.0 vs. 5.5 (g*BRCA* cohort); 12.9 vs. 3.8 (non-g*BRCA* HRD cohort); 9.3 vs. 3.9 (overall non-g*BRCA* cohort); p<0.001 across all three comparisons	11.9 vs. 5.5 in niraparib + BEV vs. niraparib alone
Median OS (mo)	42.2 (95% CI=37.7–46.2) in the CT + BEV group vs. 37.3 (95% CI=32.6–39.7) in CT group; p=0.060	PPR: 12.4 (CT alone) vs. 13.7 (CT + BEV) p=0.600; SPR: 15.6 (CT) vs. 22.2 (CT + BEV) p=0.060	Immature OS data (24% maturity) showed no detriment to olaparib (medians not reached)	(median not reached) 16.1% deaths in niraparib vs. 19.3% deaths in placebo	No treatment-related deaths during median follow-up of 16.9 months

BEV, bevacizumab; BICR, blinded independent central review; CI, confidence interval; CR, complete response; CT, chemotherapy; ECOG, Eastern Coorporative Oncology Group; g*BRCA*, germline *BRCA1/2* mutations; HRD, homologous recombination deficiency; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PPR, primary platinum resistant defined as disease progression <6 months after completion of first-line platinum therapy; PR, partial response; SPR, secondary platinum resistant defined as progression ≥6 months after first-line platinum therapy but <6 months after second-line platinum therapy.

22.2 months, though not statistically significant (p=0.060) [79], demonstrating the utility of stratifying women on the basis of PPR or SPR (**Table 4**).

The SOLO2/ENGOT-Ov21 phase III trial (NCT01874353) investigated olaparib as maintenance therapy in women with platinum-sensitive EOC and a *BRCA1/2* mutation, and at least 2 previous lines of platinum-based chemotherapy. Olaparib was associated with significantly longer median PFS (19.1 vs. 5.5 months) [80]. A recent update of this trial reported improved median OS associated with olaparib compared to placebo (51.7 vs. 38.8 months) although 10% of women in the olaparib arm and 38% of women in the placebo arm received subsequent treatment with PARPi therapy [83]. These findings have led to approval of olaparib as maintenance treatment in women with platinum-sensitive relapsed EOC and *BRCA1/2* mutations both internationally and in Australia. The ENGOT-OV16/NOVA trial (NCT01847274) of niraparib, a highly selective inhibitor of PARP1/2, showed a similarly PFS benefit in women with platinum-sensitive ovarian cancer regardless of *BRCA1/2* mutation

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or HR deficiency status, although there was significant toxicity in the maintenance setting including grade 3 or 4 adverse events [81]. Additional details of these and other trials of recurrent ovarian cancer are summarized in **Table 4**.

OVARIAN CANCER FOLLOW-UP

Ovarian cancer follow-up focuses on identifying and managing late side effects of treatment, detecting symptoms of recurrence, and managing psychosocial symptoms. The National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer recommend patient visits every 2–4 months for 2 years, then 3–6 months for 3 years, then annually after five years. Follow-up visits should include physical exam, imaging as required, evaluation of CA-125 or other tumor markers, genetic risk evaluation if required, and long-term wellness care [84]. Studies evaluating patient follow-up are limited and summarized in **Table 5**.

A phase 2 randomised controlled trial (ACTRN12620000332921) is currently recruiting (CIs Cohen, Friedlander, Obermair) and aims to enrol 150 women across 12 sites in 4 states in Australia. The study aims to demonstrate feasibility and acceptability of nurse-led telehealth compared to standard of care, and patient-reported assessment using the MOST and serum CA-125 after completion of first-line therapy with no delay in detecting of recurrence. The primary endpoint of the study is patient emotional wellbeing. Additional endpoints include cost effectiveness, the proportion of women referred for symptom management, and time to recurrence.

CONCLUSIONS AND FUTURE DIRECTIONS

HR testing in HGSOC patients is critical to treatment approaches. The EMSO Translational Research and Precision Medicine Working Group recently launched a collaborative project to define best practice for HR testing in HGSOC patients, and to provide recommendations on the clinical utility of HR tests and clinical management of HGSOC [92].

The role of PARPis is well established in the treatment of recurrent ovarian cancer with effects seen in *BRCA1/2* and HR deficiency positive women with significant effects on OS. More work is needed to understand how these drugs in combination with other targeted drugs such as bevacizumab and immunotherapy may improve outcome. PARPis in the first line for women with *BRCA1/2* mutated ovarian cancer is associated with an unprecedented improvement in median survival, suggesting curative potential for the first time for women with advanced ovarian cancer. Efforts should be made to identify all such women and ensure their access to PARPi first-line maintenance therapy.

Aiming for R0 remains the best treatment approach for patient survival while we await the result of the TRUST trial. The use of NACT-IDS does not appear to have worsened OS over time, and there is limited evidence that delayed IDS is associated with worse OS after three cycles of NACT. The judicious use of surgery timing, consideration of patient characteristics, combined with patient-tailored chemotherapy provides the best opportunity to overcome EOC biology. Further criteria are needed to stratify response patterns that may inform surgeons' decisions to ensure the best treatment outcomes that optimises patient survival

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Table 5. Ovarian cancer follow-up studies

Study	Design/aims	Results	Conclusion/recommendations
The hidden burden of anxiety and depression in ovarian cancer [85]	• Analysis of 893 EOC patients enrolled in the Ovarian cancer Prognosis And Lifestyle (OPAL) study between 2012–2015 [86] • Patients completed ≥1 follow-up questionnaires designed to evaluate lifestyle choices and the burden of anxiety and depression in women newly diagnosed with EOC	• More than 40% of patients experience clinical levels of anxiety or depressing during treatment or the first 3 years of follow-up • For 42% of those affected, this was their first experience of distress and >50% did not receive appropriate medication or psychological support	The hidden burden of anxiety and depression in this population is much greater than previously reported, but is amenable to effective intervention if recognised.
Survival of Australian women with invasive epithelial ovarian cancer: a population-based study [87]	Analysis of 1192 women diagnosed with invasive EOC to evaluate survival patterns across state-based cancer registries in Australia	Among known factors associated with poorer survival, relative socioeconomic disadvantage (HR=1.2; 95% CI=1.1–1.4) and regional-remote residence (HR=1.2; 95% CI=1.0–1.4) were also associated with poorer survival.	Possible explanations for geographic differences in EOC survival include diagnostic delay and poorer access to recommended treatments.
Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial [88]	RCT of 1,442 patients to evaluate the utility of early second-line chemotherapy in asymptomatic women based on rising CA-125 versus delayed treatment based on symptomatic relapse	No evidence of survival benefit with early treatment of relapse, greater likelihood of third-line treatment, and early deterioration in health-related QoL in the early treatment group	Study limitations • Study population and tumor histotypes were heterogeneous • No standardization of the adequacy of primary surgery or the extent of residual disease or recurrence management • 40% of patients in both arms received single-agent platinum-based chemotherapy
Evaluation of follow-up strategies for patients with epithelial ovarian cancer following completion of primary treatment (Review) [89]	Systematic review to compare the potential benefits of different strategies of follow-up in patients with EOC following completion of primary treatment	One RCT (MRC OV05/EORTC 55955, see row above) met inclusion criteria which included 529 women with data on immediate treatment of EOC relapse following rise of serum CA-125 levels versus delaying treatment until symptoms developed	This systematic review highlighted the limited evidence and the need for RCTs looking at different follow-up modalities that address both survival and the cost effectiveness, QoL and psychological outcomes.
The Measure of Ovarian Symptoms and Treatment (MOST) study [90]	A validated questionnaire designed to measure and quantify patient-reported adverse effects and symptom burden or benefit in refractory ovarian cancer; participants were a subset of 742 women enrolled in the OPAL study; questionnaire completed 6 months from diagnosis, coinciding with the completion of chemotherapy, and every 3 months up to a maximum of 3.5 years	• 61% of patients had recurred with a median time to recurrence of 11.7 months • The MOST abdominal symptom score increased 2–3 months before recurrence was diagnosed by CA-125 or clinical criteria • Only 2/452 women who recurred were diagnosed on the basis of physical examination alone	The MOST study validly quantifies PROs; these findings calls into question whether physical examination is a necessary component of routine follow-up. Further research is necessary to test-retest reliability.
Nurse led telephone follow up in ovarian cancer: a psychosocial perspective [91]	• A pilot study in Scotland of nurse led telephone follow up in ovarian cancer from a psychosocial perspective • 52 women received telephone follow up over a 10-month period • One aspect of this intervention was the opportunity for women to discuss psychosocial concerns with the clinical nurse specialist	• 42% of women discussed feelings of anxiety or depression • 33% discussed fear of disease recurrence • A majority of women (73%) over a 10-month period preferred nurse-led telephone follow-up compared to clinic-based follow-up for psychosocial support	Nurse led telephone follow-up offers an acceptable opportunity for psychosocial support for women with ovarian cancer.

CI, confidence interval; EOC, epithelial ovarian cancer; HR, hazard ratio; QoL, quality of life; RCT, randomised controlled trial; PROs, patient-reported outcomes, defined as any report of the status of a patient's health condition that comes directly from the patient, without any interpretation of the patient's response by a clinician or anyone else.

and quality of life. Timely assessment of response using a multi-modality approach will allow surgical teams to triage who will benefit from surgery.

Recent trials have demonstrated ongoing exploration of targeted therapy in women with recurrent ovarian cancer. The role of bevacizumab is very clear in primary treatment for ovarian cancer, and there is support for its use in selected patients with recurrent and platinum-resistant disease.

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Immunotherapy treatment for recurrent ovarian cancer remains disappointing at this stage, and more work is needed to determine if combinations in selected groups will yield substantial improvements in survival and quality of life.

There is a critical need for well-designed prospective studies and randomised controlled trials evaluating different follow-up modalities that address not only survival, but also cost effectiveness, quality of life and psychological effects of ovarian cancer treatment.

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SUPPLEMENTARY MATERIAL

Data S1

BRCA1 and *BRCA2* tissue testing: a laboratory perspective

Click here to view

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