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Review Article

Novel treatment options in platinum-sensitive recurrent ovarian cancer: A review

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HIGHLIGHTS

- The standard of care for the treatment of platinum-sensitive recurrent ovarian cancer is platinum-combination chemotherapy.
- Platinum therapy should not be delayed in order to prolong the progression free interval.
- This review discusses various angiogenesis inhibitors including bevacizumab, cediranib, and trebananib.
- This review assesses the benefits, side effects, and future development of PARPi in platinum-sensitive recurrent patients.
- More research is necessary to optimize molecularly targeted therapy leading to improved survival for ovarian cancer patients.

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ABSTRACT

Epithelial ovarian cancer (EOC) is the leading cause of death due to gynecologic malignancy. The majority of advanced stage EOC patients, even those who respond well to frontline therapy, will ultimately recur and succumb to their disease. In platinum-sensitive EOC patients, or those who recur ≥6 months from initial diagnosis, treatment of recurrent disease has traditionally consisted of repeat platinum-based chemotherapy. Secondary cytoreduction remains controversial. Due to recent advances in molecularly targeted treatment options, outcomes for advanced stage EOC patients are significantly improving and hold great promise. This review discusses pivotal trials establishing platinum-based combination chemotherapy as the standard of care and addresses the utility of increasing a patient's platinum-free interval. It then discusses the role of anti-angiogenesis therapeutics, specifically bevacizumab, cediranib, and trebananib and their side effects. Lastly, it reviews key trials for the three poly-adenosine diphosphate [ADP]-ribose polymerases (PARP) inhibitors that have been FDA-approved for maintenance therapy in platinum-sensitive recurrent EOC: olaparib, rucaparib, and niraparib. This review concludes with a discussion regarding ongoing and future clinical trials.

Contents

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1. Introduction

Epithelial ovarian cancer (EOC) ranks first in gynecologic cancer deaths and fifth in cancer deaths among women overall [1]. Treatments have evolved over recent years with advancements in surgery and chemotherapy resulting in a decrease in cancer mortality of over 30% [1]. Despite these advances, >80% of patients with advanced-stage EOC will recur and die within 5 years [2,3].

Surgery accompanied by chemotherapy with platinum and taxane agents has been established as the standard of care in the treatment of EOC [4,5]. Traditionally, the response to chemotherapy after initial recurrence is dependent on the platinum-free interval (PFI) and should be replaced by treatment-free interval from last platinum, last non platinum therapy or last biological therapy in future trials [6]. Platinum-sensitive disease refers to a PFI of at least 6 months, but can be >12 months [7,8]. Patients with platinum-sensitive disease tend to have better treatment response and thus prognosis compared to their platinum-resistant counterparts. Given the majority of patients have platinum-sensitive recurrent disease, this group is an important focus of novel therapies in an attempt to improve survival [2,3].

Here we review recent developments in the treatment of platinum-sensitive recurrent EOC, specifically secondary cytoreduction, platinum-based chemotherapy, anti-angiogenesis targeted therapies, and poly-adenosine diphosphate [ADP]-ribose polymerases (PARP) inhibitors (PARPi).

2. Surgery for recurrent ovarian cancer

Secondary cytoreduction in platinum-sensitive recurrent EOC remains controversial due to mixed results in overall survival (OS) benefit. A meta-analysis in platinum-sensitive EOC patients demonstrated a 3 month increase in median OS for each 10% increase in the proportion of patients undergoing cytoreduction [9]. A systematic review revealed an increased OS in platinum-sensitive patients who were cytoreduced to no residual macroscopic (R0) disease compared with those who had any visual disease (HR 3.59, 95% CI 2.45–5.34) [10]. Yet, due to inherent limitations of this type of research it remains unclear if this effect is exclusively due to surgery versus tumor biology.

Currently, there are three phase III randomized clinical trials (RCT) evaluating this clinical question: an Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) trial entitled descriptive evaluation of preoperative selection criteria for operability in recurrent ovarian cancer (DESKTOP) III (NCT01166737), Gynecologic Oncology Group (GOG) 213 (NCT00565851), and the Netherlands SOCceR trial (NTR3337). Preliminary results from DESKTOP III presented at the American Society of Clinical Oncology (ASCO) Meeting in 2017, demonstrated that patients with platinum-sensitive recurrent EOC who underwent secondary cytoreduction versus a platinum-containing second line therapy experienced a progression-free survival (PFS) benefit of 5.6 months (19.6 vs 14 months; $p < 0.001$) and longer time to the start of subsequent chemotherapy (21 vs 13.9 months; $p < 0.001$). In subset analysis of the PFS by surgical outcome, the R0 patients had the best PFS of 21.2 months compared to patients with residual tumor of 13.7 months versus no surgery patients of 14.0 months confirming that the biology of the recurrent disease is the critical factor. The primary endpoint OS is still not mature [11]. At ASCO 2018, the results of GOG 213 were presented and women who underwent secondary cytoreduction followed by chemotherapy did not show a benefit in PFS or OS compared to women who did not undergo surgery and received chemotherapy instead [12]. The main difference in GOG 213 and DESKTOP III was the high rate of maintenance bevacizumab of 84% vs 20% respectively. The SOCceR trial completed accrual in June of 2017, but has not been reported [13]. Based on the current literature, an attempt at R0 secondary cytoreduction remains important, especially since bevacizumab seems to offset the advantage of surgery based on GOG 213.

3. Platinum based combination chemotherapy

Among those with platinum-sensitive disease, a large amount of heterogeneity in PFI exists. Clinically, this is important because the degree of secondary response to a platinum agent seems to improve with longer PFI [8].

Traditionally, platinum monotherapy was given due to ease of administration and high tolerability due to reduced cumulative toxicities (i.e. neuropathy) from repeat treatment with taxane-based chemotherapy [14]. Single-agent carboplatin has been the preferred choice over other platinum agents given its similar efficacy and more favorable toxicity profile. However, to improve survival outcomes, trials began testing the role of platinum combination chemotherapy using agents with different mechanisms of action. ICON4/OVAR 2.2 was the first phase III RCT comparing platinum monotherapy to platinum and paclitaxel therapy [3]. OS and PFS were improved with combination therapy (29 vs 24 months, HR 0.82, $p = 0.02$; 12 vs 9 months, HR 0.76, $p < 0.001$). Moderate to severe alopecia (86% vs 25%) and neurologic adverse events (20% vs 1%) were more common in the experimental arm. Of note, 40% of patients received paclitaxel as first-line therapy, potentially underestimating the magnitude of adverse effects. Due to the improved OS demonstrated by this trial, the platinum-taxane combination was often used as a reference group in subsequent trials (Table 1).

In an attempt to decrease the toxicity of platinum-taxane regimens, alternative platinum combinations have been studied. A phase III RCT evaluating gemcitabine plus carboplatin (GC) versus carboplatin demonstrated improved PFS of 8.6 months versus 5.8 months in favor of combination therapy (HR 0.72, $p = 0.003$), but no difference in OS [15]. As expected, myelosuppression was significantly more common with combination therapy. Subsequently, CALYPSO was a non-inferiority RCT comparing carboplatin and paclitaxel (CP) with carboplatin and pegylated liposomal doxorubicin (PLD) (CD) [16]. PFS was improved in the CD arm (11.3 vs 9.4 months, HR 0.82, $p = -0.005$) without an OS benefit (HR 0.99, $p = 0.87$) [17]. Grade 2 or greater alopecia (83.6% vs 7%),

Table 1
Landmark chemotherapy trials in platinum-sensitive recurrent ovarian cancer.

Study	Primary outcome	Study groups	PFS (months)	HR (95% CI)	*p*-value	OS (months)	HR (95% CI)	*p*-value
ICON4 [2]	OS	Carbo Carbo/Taxol	10 13	0.76 (0.66–0.89)	0.0004	24 29	0.82 (0.69–0.97)	0.02
AGO [15]	PFS	Carbo Carbo/Gem	5.8 8.6	0.72 (0.58–0.90)	0.003	17.3 18.0	0.96 (0.75–1.23)	0.73
CALYPSO [16,17]	PFS	Carbo/Taxol Carbo/PLD	9.4 11.3	0.82 (0.72–0.94)	0.005	30.7 33.0	0.99 (0.85–1.16)	0.94
OCEANS [25,26]	PFS	Carbo/Gem/Placebo Carbo/Gem/Bev	8.4 12.4	0.48 (0.39–0.61)	<0.0001	32.9 33.6	0.95 (0.77–1.17)	0.65

Abbreviations: Carbo, carboplatin; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; Gem, Gemcitabine; PLD, pegylated liposomal doxorubicin; Bev, bevacizumab.

hypersensitivity reactions (18.8% vs 5.6%), and sensory neuropathy (26.9% vs 4.9%) were more common with CP. Hand-foot syndrome (12.0% vs 2.2%), nausea (35.2% vs 24.2%), and mucositis (13.9% vs 7%) were more common with CD. Phase I/II clinical trials studying the combination of topotecan and carboplatin in platinum-sensitive disease have demonstrated tolerability, but further studies are needed to test efficacy compared to other platinum combinations [18].

Given increased toxicities with platinum-based combination therapy as well as only one RCT demonstrating improvement in OS, Raja et al. published a meta-analysis evaluating the size of benefit of combination treatment [19]. Combination therapy was associated with improved OS (HR 0.80, $p = 0.05$) and PFS (HR 0.68, $p < 0.001$). Subgroup analyses demonstrated no difference in the effect of treatment by previous paclitaxel exposure, PFI (6–12 vs 12 months), or number of previous lines of chemotherapy. Adverse events and quality of life (QOL) were not evaluated.

Landmark chemotherapy trials in patients with platinum sensitive ovarian cancer are summarized in Table 1.

4. Prolonging the PFI

Prolonging the PFI with a non-platinum agent has been hypothesized to enhance survival benefits by improving the response to subsequent platinum-based chemotherapy [4,14,20]. A post hoc analysis of OVA-301, a phase III RCT evaluating trabectedin plus PLD versus PLD alone, supports this hypothesis [21]. In their exploratory analyses, subsequent therapies beyond study protocol and survival outcomes were reported as were subset analyses based on platinum sensitivity. They showed that the platinum-sensitive patients demonstrated that the combination delayed subsequent platinum treatment by 2.5 months and led to improved PFS (7.4 vs 5.5 months, HR 0.65, $p = 0.015$) and OS (23 vs 17.1 months, HR = 0.59, $p = 0.0015$) [22]. Although exploratory, these findings support the hypothesis that expanding the PFI with a non-platinum agent, for example trabectedin plus PLD, may allow for improved responses to retreatment with platinum-based chemotherapy. Differing results came from MITO8, an international, multi-center, open-label phase III RCT designed to determine if prolonging the PFI by introducing a non-platinum based chemotherapy would improve sensitivity to subsequent platinum treatment [23]. Patients who recurred with a PFI of 6–12 months were assigned to non-platinum-based chemotherapy followed by platinum-based chemotherapy at subsequent relapse (experimental arm) or to the standard sequence of platinum-based chemotherapy followed by non-platinum-based chemotherapy. Non-platinum-based chemotherapy consisted of PLD in >85% of cases. PFI was prolonged in the experimental arm (7.8 vs 0.01 months). There was no OS benefit, and QOL and PFS were significantly worse in the experimental arm. This trial concluded that platinum-based chemotherapy should not be delayed in patients with partially platinum-sensitive EOC. The INOVATYON trial is evaluating the combination of trabectedin and PLD vs CD (NCT01379989), and although accrual has completed there are no results.

5. Angiogenesis targets

Angiogenesis is necessary for tumor-cell survival, growth, and metastasis. Therefore, inhibition of angiogenesis can add therapeutic benefit and work synergistically with existing therapies. Angiogenesis is driven by key factors: platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), angiopoietin-Tie2 receptor, and fibroblast growth factor (FGF) [24]. Targeting these key factors will antagonize angiogenesis.

5.1. Bevacizumab

Bevacizumab (Bev) is a humanized monoclonal antibody directed against VEGF. OCEANS was a phase III RCT evaluating bevacizumab with GC compared to GC plus placebo in platinum-sensitive recurrent EOC [25]. Maintenance bevacizumab or placebo was administered until progression or unacceptable toxicity. Bevacizumab resulted in superior PFS (12.4 vs 8.4 months, HR 0.485, $p < 0.001$) with no difference in OS (33.6 vs 32.9 months, HR 0.95, $p = 0.65$) [26]. Notably, many patients received subsequent chemotherapy and >30% of placebo patients received bevacizumab at some point after progression which may have affected OS. Grade 3 or higher hypertension (17.4% vs <1%) and proteinuria (8.5% vs <1%) were more common in the bevacizumab arm. Two patients in the bevacizumab arm had gastrointestinal perforation after study treatment was completed. Subgroup analyses evaluating PFI (6–12 vs 12–24 vs. >24 months) demonstrated persistent, significant improvement in PFS [25,26].

GOG 213 was a subsequent phase III RCT evaluating CP versus CP plus bevacizumab in platinum-sensitive recurrent EOC as well as the benefit of secondary cytoreduction [12]. Patients were randomized to either CP every 3 weeks or CP plus bevacizumab with bevacizumab maintenance (CP + Bev arm) until disease progression or unacceptable toxicity. The primary endpoint was OS. PFS was longer in the CP + Bev arm (13.8 vs 10.4 months, HR 0.63, $p < 0.0001$). Intention to treat (ITT) analysis demonstrated no difference in OS (CP + Bev: 42.2 vs CP: 37.3 months, HR 0.89, $p = 0.056$). It has been argued that underestimation of the control arm's performance led to this trial having a negative primary outcome. It is remarkable that this trial demonstrated preservation of the PFS effect for >24 months post-progression. Additionally, review of the data demonstrated incorrectly reported PFI (i.e. intervals were reported from last maintenance treatment as opposed to the last cycle of platinum-based chemotherapy). Sensitivity analysis based on corrected treatment-free interval stratification demonstrated improved OS in the CP + Bev group (HR 0.82, $p = 0.045$). More toxicity was observed with concomitant treatment; 28% of patients in the CP + Bev group experienced a serious adverse event compared to 11% of patients who received CP alone. Adverse events of grade 3/4 that were more frequent in the CP + Bev group included thromboembolism (4% vs 1%), abdominal pain (12% vs 0%), nausea (9% vs 3%), small bowel obstruction (6% vs 3%), gastrointestinal perforation/fistula/abscess (15% vs 4%),

hypertension (12% vs 1%), fatigue (8% vs 2%), and proteinuria (8% vs 0%). While there was more toxicity observed with concomitant treatment, no new safety signals were identified and there was no difference in QOL as reported by Function Assessment of Cancer Therapy-Ovary (FACT-O) scores between groups.

Given an increasing number of women are receiving bevacizumab with initial therapy, it is important to understand the role of second-line bevacizumab in this group. MITO-16 is a phase III RCT evaluating bevacizumab in combination with chemotherapy in platinum-sensitive recurrent EOC patients who received bevacizumab first-line (NCT01706120). The primary endpoint is PFS. Preliminary results demonstrate improved PFS (8.8 vs 11.8 months, HR 0.51, $p < 0.0001$) in patients who were retreated with bevacizumab [27]. Data for OS is still immature. As expected, grade ≥ 3 hypertension (28% vs 10%) and proteinuria (4% vs 0%) are more frequent with bevacizumab treatment.

5.2. Cediranib

Cediranib is an oral VEGF receptor and c-KIT inhibitor and has shown antitumor activity in recurrent EOC in phase I/II studies. ICON6 was a phase III RCT consisting of three study arms: chemotherapy/placebo with placebo maintenance (arm A), cediranib/chemotherapy with placebo maintenance (arm B), cediranib/chemotherapy with cediranib maintenance (arm C) [28]. PFS was significantly improved in arm A versus C (11.0 vs 8.7 months, HR 0.56, $p < 0.0001$). OS at 25 months follow-up was improved in the cediranib maintenance group compared to the placebo group, but this was not statistically significant (27.3 vs 19.9 months, HR 0.85, $p = 0.21$) [29]. Twenty-seven percent of patients in arm B and 40% of patients in arm C discontinued cediranib due to toxic effects most notably diarrhea, neutropenia, hypertension, hypothyroidism, and voice changes [28]. QOL data suggested no significant differences between the groups 1 year after initial treatment [30].

5.3. Trebananib

Trebananib is a peptide that inhibits angiopoietin-1 and -2 which are involved in angiogenesis. Given the alternative mechanism of action compared to traditional VEGF receptors the adverse events are distinct and possibly more favorable. TRINOVA-1 evaluated patients with recurrent disease <12 months from previous platinum treatment and stratified by platinum-sensitive and platinum-resistant or refractory disease [31]. Patients were randomized to receive weekly paclitaxel and trebananib or weekly paclitaxel and placebo. PFS was longer in the trebananib group (7.2 vs 5.4 months, HR 0.66, $p < 0.001$). Subgroup analyses demonstrated this difference was consistent in platinum-sensitive patients with PFI > 6 months and ≤12 months (HR 0.66, CI 0.52–0.84). OS was not different between the two groups (19.3 vs 18.3 months, HR 0.95, $p = 0.52$) and this remained true when stratified for platinum sensitivity (HR 0.93, CI 0.73–1.19). Grade 3 adverse events were similar between groups (56% vs 54%). The main side effect experienced by the trebananib group versus control was diffuse edema (64% vs 28%), leading to an 8% discontinuation rate.

5.4. Side effects of anti-angiogenic drugs

While anti-angiogenic drugs are generally well tolerated, they do have a specific side-effect profile due to their mechanism of action. The most common toxicities are described above and include hypertension, proteinuria, hemorrhage, thrombotic events, poor wound healing, and possible gastrointestinal perforation. VEGF receptor inhibitors such as cediranib are associated more with increased fatigue, diarrhea, and hypertension compared to VEGF monoclonal antibody inhibitors such as bevacizumab which are more associated with proteinuria, hypertension, gastrointestinal issues, and thromboembolism. No particular antihypertensive agent is superior in management, but it is important to maintain a blood pressure < 140/90 mm Hg. If proteinuria is ≥2+ on urinalysis, a 24 h urine protein collection should be obtained; if there is >2 g/24 h bevacizumab should be stopped and restarted when <2 g/24 h. If there is ≥3 g/24 h, then bevacizumab needs to be permanently discontinued. There is a bevacizumab Federal Drug Agency black box warning recommending discontinuation in the setting of gastrointestinal perforation, wound dehiscence, or any type of hemorrhage [32].

6. PARP inhibitors (PARPi)

PARPi are one of the most promising targeted agents currently in clinical trials for EOC and include olaparib (AZD2281), niraparib (MK4827), rucaparib (CO338, AGO14699, and PF01367338), veliparib (ABT-888), and talazoparib (BMN 673). For purposes of this review we will focus primarily on the first three, which progressed through preclinical and early phase trials showing single-agent anti-cancer activity in *BRCA* deficient cells and ultimately emerged from phase III trials to receive FDA approval in recurrent EOC and platinum-sensitive maintenance therapy. Through robust trial designs PARPi are expanding their role in both the presence and absence of a germline *BRCA* mutation and platinum sensitivity [33].

6.1. Mechanism of PARPi

Synthetic lethality occurs when there is a potent and lethal synergy between two otherwise non-lethal events. PARP enzymes are involved in DNA repair through the base-excision repair pathway, keeping the low-fidelity nonhomologous-end joining DNA repair machinery in check [33,34]. PARP inhibition leads to persistence of spontaneously occurring single-strand breaks and induction of double-stranded breaks (DSBs) after stalling and collapse of the DNA replication forks. These DSBs cannot be repaired by cells defective in homologous repair pathway, such as *BRCA*-mutated or homologous recombination deficient (HRD) cells, thereby resulting in synthetic lethality. Another mechanism of PARP inhibition is PARP trapping which occurs when the PARP enzyme is trapped on the DNA by a PARPi thereby interfering with DNA replication [33–37].

6.2. Clinical impact

PARPi are selectively potent against cells with biallelic *BRCA*1 or 2 deficiency, and in clinical trials have shown antitumor activity and extend PFS compared with placebo among patients with or without a *BRCA* mutation [35,38–41]. Approximately 15% of all EOC harbor a germline *BRCA* mutation, 6% a somatic *BRCA* mutation, and 20% a mutation in, or epigenetic silencing of another homologous recombination (HR) gene [42,43]. Furthermore, approximately 50% of all high-grade serous ovarian carcinomas (HGSCs) are estimated to have HRD [43]. *BRCA*ness gene-expression profile in HGSOC patients have been studied and correlated with responsiveness to both platinum-based chemotherapy and PARPi [42,44,45]. However, which *BRCA* wild-type cancers are most likely to respond to a PARPi remains unknown. Below is a summary of FDA approved PARPi and associated landmark clinical trials.

6.3. Olaparib

Olaparib is an oral PARP-1, PARP-2 and PARP-3 inhibitor that received FDA accelerated approval in December 2014 as 4th line treatment and beyond monotherapy for germline *BRCA* mutant EOC patients [38,39,46–51]. FDA approved olaparib capsules first and later approved olaparib tablets; however, they are not interchangeable. Olaparib is one of the most well studied PARPi, and shown to be active among sporadic, HGSOC with known germline *BRCA* mutations as well as in the maintenance setting for women with platinum-sensitive recurrent EOC. Initial phase I/II testing used the capsule formulation, but

more recently all phase III studies of olaparib involve the tablet formation, which requires fewer pills [50].

A landmark study that led to an FDA registration strategy for PARPi to be used in maintenance therapy in patients with platinum-sensitive recurrent EOC was Study 19, a randomized, double-blind, placebo controlled, phase 2 study evaluating maintenance treatment with olaparib in patients with platinum-sensitive recurrent HGSOC [47]. Women were eligible if they had received ≥2 platinum-based regimens and achieved at least a partial response (PR) to their most recent platinum-based regimen. The primary endpoint, PFS was 3.6 months longer in the treatment group (8.4 vs 4.8 months; HR 0.35, 95% CI 0.25–0.49; $p < 0.001$), and although not powered to show an OS difference, the data cutoff for the OS analysis was about 7 years after study initiation. Ledermann et al. showed an OS advantage with maintenance olaparib versus placebo (29.8 vs. 27.8 months, HR 0.73, 95% CI 0.55–0.96, $p = 0.025$), which did not meet the required threshold for statistical significance [48]. This effect was predominantly driven by the *BRCA*-mutated group who received the greatest OS benefit from olaparib, HR 0.62 (95% CI 0.41–0.94, p = 0.025). Overall olaparib was well tolerated and 11 of 74 patients with a *BRCA* mutation received maintenance olaparib for ≥5 years. Common adverse events in the olaparib group versus placebo included nausea (68% vs. 35%), fatigue (49% vs 38%), vomiting (32% vs. 14%), and anemia (17% vs. 5%). There were no differences in QOL.

Although exciting that this was first trial to report data on PARPi maintenance therapy in patients with platinum-sensitive recurrent EOC, it was not without limitations. The study design and inclusion criteria did not allow for comparisons between patients with *BRCA* germline mutations vs those with a "*BRCA*ness" phenotype, nor did it have a translational component to identify HRD biomarkers, a methodology that was later explored in trials involving rucaparib (ARIEL2 and ARIEL3) or niraparib (NOVA) [41,52–54].

SOLO2 followed Study 19, and was designed as a double-blind, multicenter study in which patients were randomized (2:1) to receive olaparib 300 mg tablets bid or placebo. It included patients with recurrent HGS or endometrioid ovarian cancer, including primary peritoneal and/or fallopian tube cancer, who had a known or suspected deleterious *BRCA*-mutation and had PR or complete response (CR) following completion of at least 2 lines of platinum-based chemotherapy. The primary outcome was PFS by blinded independent central review (BICR) [49].

Results from SOLO2/ENGOT-Ov21 represent the first phase III data for the tablet formulation of olaparib as monotherapy in patients with platinum-sensitive recurrent EOC. Two hundred ninety-five patients with germline or somatic *BRCA* 1/2 mutations were enrolled, but confirmatory germline testing with two blood samples were required. The primary endpoint, PFS, was evaluated by investigator assessment and BICR. Exceeding the PFS benefit demonstrated in Study 19, SOLO2 showed that PFS in the olaparib maintenance group versus placebo was significantly longer (19.1 vs. 5.5 months, HR 0.30, 95% CI 0.22–0.41; $p < 0.0001$). The tablet formulation of olaparib was more convenient for patients, reducing the pill burden from 16 capsules to 4 tablets per day while maintaining efficacy. Overall, this treatment was tolerable with only 18% of patients in the olaparib group experiencing a serious adverse event, the most common being anemia (4%), abdominal pain (2%), and intestinal obstruction (2%). One patient developed acute myeloid leukemia (AML) with an outcome of death. A prespecified subgroup analysis of PFS in 53 patients who had previously received bevacizumab prior to their final platinum regimen showed that bevacizumab did not compromise the beneficial treatment effect of olaparib (17 vs 10.8 months, HR 0.14, 95% CI 0.007–0.28; $p < 0.0001$). Among the secondary outcomes, time to first and second subsequent therapy was also significantly improved in the olaparib maintenance group. Also, there was no detrimental effect of olaparib on patient-reported outcomes over time as assessed by the FACT-O [50]. OS data remain immature at this time. On August 17, 2017, the FDA granted expanded approval of olaparib tablets for maintenance therapy in EOC patients who have achieved either a CR or PR to platinum-based chemotherapy irrespective of *BRCA* status without further data on the *BRCA* wild-type population [51].

6.4. Rucaparib

Rucaparib is another PARP-1, PARP-2, and PARP-3 oral inhibitor. On December 19, 2016, it became the only PARPi to receive FDA Breakthrough Therapy designation for third-line treatment of patients with platinum-sensitive *BRCA*-mutated (germline and/or somatic) advanced EOC [55]. In conjunction with the drug approval, FDA approved the Foundation Focus CDxBRCA test (Foundation Medicine Inc.), the first FDA-approved next-generation sequencing (NGS)-based companion diagnostic to predict rucaparib sensitivity.

Building upon prior studies which showed extended PFS with PARPi monotherapy compared to placebo in patients with or without a *BRCA* mutation [40], the aim of ARIEL2 was to identify molecular predictors of rucaparib sensitivity in patients with platinum-sensitive recurrent high-grade EOC. Designed as an international, multicenter, two-part study, ARIEL2 Part 1 assessed the ability of tumor genomic loss of heterozygosity (LOH), quantified with a NGS assay, to predict response to rucaparib, with the primary endpoint of PFS [52]. It involved 206 patients with HGS or endometrioid cancer who received one or more prior platinum-based chemotherapy and whose last treatment regimen was platinum-based. Patients in ARIEL2 Part 1 were classified into one of three predefined HRD subgroups based on the tumor mutational analysis: 1) *BRCA* mutant (deleterious germline or somatic); 2) *BRCA* wild-type and LOH high or 3) *BRCA* wild-type and LOH low. Results from a phase I/II study of rucaparib established the efficacy and safety in women with relapsed, platinum-sensitive, high-grade EOC with a germline *BRCA* mutation. They found that patients with a germline or somatic *BRCA* mutation (16.6 months; 95% CI 13.4–22.9) or wild-type *BRCA* with high LOH (13.6 months; 95% CI 10.9–16.2) had longer PFS and more objective responses with rucaparib than did patients with wild-type *BRCA* and low LOH (10.8 months; 95% CI 8.3–11.4). This lends support for the role of high genomic LOH as defined by Foundation Medicine's T5 assay, as a predictive biomarker for sensitivity to rucaparib treatment. Furthermore, ARIEL2 Part 1 showed that the mutation and methylation of other homologous recombination-related genes, such as RAD51C/D, can also be associated with high genomic LOH in *BRCA* wild-type tumors and with rucaparib response.

Adverse events were frequent and led to dose reductions in 39% of patients, the most common grade 3 events being anemia or decreased hemoglobin (22%) and elevation in alanine aminotransferase or aspartate aminotransferase (12%). Common serious events included small intestinal obstruction (5%), and progression of disease (5%). Nine percent withdrew from the study as a result of a treatment-emergent adverse event; however, no treatment related deaths occurred [52].

Cited limitations of this study revolve around generalizability of results and validity of the HRD assay, both of which were addressed in subsequent trials. ARIEL2 Part 2 prospectively tested the HRD assay to assess for rucaparib treatment response in patients with platinum-sensitive, platinum-resistant, or platinum-refractory recurrent EOC; who have received at least three but no more than four prior chemotherapies; and have had a treatment-free interval of no >6 months following first line chemotherapy. ARIEL2 demonstrated the greatest benefit in platinum-sensitive patients who had a germline or somatic mutation compared to the platinum-resistant/refractory patients [53]. Evaluation of the same HRD assay using the LOH cutoff discriminator that was optimized in ARIEL2 Part 1 was performed in a more robust analysis planned in ARIEL3 [41,52] to confirm its predictive versus prognostic value for sensitivity to rucaparib treatment. ARIEL3 was a randomized double-blind, placebo-controlled phase III trial assessing rucaparib maintenance versus placebo in 564 patients with platinum-sensitive recurrent EOC who had received at least two prior platinum-based chemotherapy regimens and had achieved CR or PR to their last

platinum-based regimen. Patients were randomly allocated 2:1 to receive rucaparib 600 mg orally bid vs placebo, stratified by HRD mutation status. Three nested cohorts were defined for step-down analysis of the primary outcome, median PFS: tumor *BRCA* mutant (germline or somatic); HRD mutated (including *BRCA* wild-type with high genomic LOH); and the ITT population. PFS in patients with a *BRCA*-mutant carcinoma was 16.6 months (95% CI 13.4–22.9) who received rucaparib vs 5.4 months (95% CI 3.4–6.7) placebo (HR 0.23, 95% CI 0.16–0.34; $p < 0.0001$). Among patients with a HRD carcinoma, median PFS was 13.6 versus 5.4 months (HR 0.32, 95% CI 0.24–0.42; $p < 0.0001$). For the ITT population, the median treatment duration was 10.8 versus 5.4 months ($p < 0.0001$) in the rucaparib and placebo group respectively. Grade 3/4 adverse events were 56% in the rucaparib group vs 15% in the placebo group, the most common being anemia or decreased hemoglobin (19% vs 1%) and increased alanine or aspartate aminotransferase (10% vs. 0%) [41]. Based on these results, the FDA approved rucaparib for maintenance on April 6, 2018 [55].

6.5. Niraparib

Niraparib is an inhibitor of PARP-1 and PARP-2 enzymes, but is particularly a potent inhibitor of PARP-2. In March 27, 2017 it was FDA approved for maintenance therapy in all women with recurrent EOC who have previously responded to platinum-based chemotherapy. Niraparib is metabolized via carboxylesterases forming an inactive metabolite. Unlike the other PARPi, niraparib does not induce nor inhibit the cytochrome P450 enzymes leading to less potential for drug-drug interactions. The drug's mean half-life is 36 h enabling the once daily dosing of 300 mg. An additional pharmacologic characteristic unique to niraparib is the ability to cross the blood brain barrier which causes the inhibition of norepinephrine and dopamine through binding to transporters of dopamine, norepinephrine, and serotonin [56].

The ENGOT-OV16/NOVA trial was the pivotal phase III maintenance study of niraparib in platinum-sensitive patients that led to not only to the first US approval of maintenance therapy in EOC, but also the use of PARPi in all EOC patients regardless of the presence of a germline or somatic *BRCA* mutation [54]. Eligible patients included women with platinum-sensitive disease who had either a germline *BRCA* mutation or HGSC histology and completed 2 or more prior lines of platinum-based chemotherapy. Patients must have achieved a CR or PR after receiving 4–6 cycles of platinum-based chemotherapy and enrolled within 8 weeks of their last chemotherapy. A prerequisite was an absence of measurable disease >2 cm at study entry unlike the ARIEL3 trial where approximately 15–19% of the population had bulky disease [41]. Ultimately, 553 patients were included in two cohorts: a germline *BRCA* mutated cohort ($n = 203$) and a non-germline *BRCA* mutated cohort ($n = 350$) as determined by the Myriad BRCAnalysis test. Randomization was 2:1 with patients receiving niraparib 300 mg or placebo daily until disease progression. Crossover was not permitted. There were three PFS endpoints: PFS in the germline *BRCA*-mutated cohort, PFS in the non-germline *BRCA*-mutated cohort, and PFS in the HRD-positive subgroup within the non-germline *BRCA*-mutated cohort. HRD status was determined by the Myriad my Choice HRD™ test. The statistical design dictated hierarchal testing whereby PFS was compared simultaneously in the germline *BRCA* mutated cohort and the HRD-positive subgroup of the non-germline *BRCA* mutated cohort. If results were significant in the HRD positive subgroup, PFS was to be compared between treatment arms in the entire non-germline *BRCA* mutated cohort. PFS was significantly improved with the use of niraparib in all three cohorts compared to placebo. As expected, the magnitude of treatment effect appeared greatest in patients with germline *BRCA* mutation or HRD positive tumors. The PFS HR was 0.27 in the *BRCA* mutant population (21 vs 5.5 months, $p < 0.0001$); PFS HR was 0.38 in the HRD positive subgroup of the non-germline *BRCA* mutated cohort (12.9 vs. 3.8 months, $p < 0.0001$); and PFS HR was 0.45 in the overall non-germline *BRCA* mutated cohort (9.3 vs 3.9 months, $p < 0.001$). In order to prove that the PFS benefit in the overall non-germline *BRCA* cohort was not entirely driven by the benefit from the HRD-positive tumors, an exploratory PFS analysis in this subgroup was performed with a PFS HR of 0.58 (6.9 vs. 3.8 months, $p = 0.02$) [54]. Additionally, for a small pooled group of patients who progressed regardless of germline *BRCA* status, there was no reduction in benefit of niraparib treatment on the effectiveness of subsequent chemotherapy (HR = 1.02) [57]. Patients who received niraparib as maintenance treatment retained QOL by the FACT-O Symptom Index comparable to placebo [58]. OS data remains immature, but in a recent update the estimated probability of PFS at 2 years in niraparib treated germline *BRCA* mutated cohort was 42% [59].

Niraparib's side effects parallel many of the toxicities of the PARPi class. However, there are some unique hematological, gastrointestinal, respiratory and cardiovascular toxicities. In the NOVA trial, hematologic adverse events accounted for the majority of grade 3/4 toxicity events and commonly led to dose discontinuation, interruption, or modification. Grade 3/4 thrombocytopenia occurred in 34% of patients and usually occurred in the first couple of cycles. Grade 3/4 anemia and neutropenia happened 25% and 20%, respectively. With dose modifications, only 3%, 2%, and 1% of patient discontinued niraparib for thrombocytopenia, neutropenia, or anemia respectively. An exploratory analysis of the hematologic adverse events revealed that patients with a baseline body weight < 77 kg or platelet count of <150 K were at higher risk to develop grade 3 thrombocytopenia and dose reduction [60]. Although the niraparib starting dose is 300 mg orally daily, the average dose delivered in the first 2 months of therapy was 206 mg [59]. The recommended dose for patients who meet either of the above criteria is to start at 200 mg daily and to get weekly complete blood count for the first month. If no hematologic events occur in the first 2–3 months, a clinician could consider dose escalation with close monitoring of blood work. Importantly, despite dose modifications, the efficacy of niraparib was maintained [60].

Grade 3/4 hypertension occurred in 9% of patients [56]. Hypertensive patients should check and record their blood pressure regularly so that the need for dose adjustments or anti-hypertensive agents can be appropriately assessed. With patient education and monitoring of complete blood counts, the majority of the side effects can be managed effectively with a minority of patients requiring discontinuation of niraparib.

6.6. Choice of PARPi

Considerations that impact provider selection of which PARPi to prescribe is often based on the number of prior chemotherapy lines, ease of dosing options, side effect profile that may exacerbate any pre-existing toxicities, provider experience with various PARPi, and knowledge of patient's *BRCA* status, LOH status and/or other HRD-related genes. Table 2 summarizes key clinical factors of PARP inhibitors. Table 3 summarizes adverse effects per the three landmark PARPi clinical trials.

With regards to number of prior chemotherapy lines, original FDA approval for olaparib and rucaparib distinctly specify three or more vs. two or more previous chemotherapies respectively. The completion of phase III trials involving PARPi for maintenance therapy in the setting of recurrent EOC after response to platinum therapy have provided promising results that are changing the course of disease for these patients. To summarize, Study 19 and SOLO2 studying olaparib, NOVA studying niraparib and ARIEL3 studying rucaparib support the clinical benefit of using PARPi as maintenance therapy for platinum-sensitive recurrent EOC patients who are responding to platinum-based chemotherapy [40,41,47,49,54]. However, NOVA and ARIEL3 extends this indication even further to patients regardless of *BRCA* status and LOH/HRD status with phase III data and thereby utilizing these markers as predictor of response to treatment. It cannot be emphasized enough that differences between trials do not allow for direct comparisons. Notable discrepancies in the inclusion criteria are *BRCA* mutation status,

Table 2
Clinical aspects of PARP inhibitors.

	Olaparib [40,49,51]	Rucaparib [41,55]	Niraparib [54,56]
Dose	400 mg BID (capsules) 300 mg BID (tablets)	600 mg BID (tablets)	300 mg QD (capsules)
Dosage forms	50 mg (capsules) 100 mg, 150 mg (tablets)	200 mg, 250 mg, 300 mg (tablets)	100 mg (capsules)
Metabolism (major enzymes)	CYP3A4	CYP2D6	Carboxylesterase
Dose adjustments	Renal impairment CYP3A inhibitors	None	None
Dose Reductions for SEs	250 mg BID 200 mg BID	500 mg BID 400 mg BID 300 mg QD	200 mg QD 100 mg QD
Monitoring	-CMP baseline/monthly -CBC baseline/monthly	-CMP baseline/monthly -CBC baseline/monthly	-CMP baseline/monthly -CBC baseline, weekly for first month and then monthly -BP and HR monthly x 1 year
Previous lines of PBC chemotherapy	≥2	≥2	≥2
Patient population in Phase III	PS relapsed HGS or HG endometrioid cancer EOC, with *BRCA*1/2 mut	PS relapsed HGS or endometrioid EOC with *BRCA*1/2 mut, HRD positive	PS relapsed HGS EOC with *BRCA*1/2 mut, HRD-positive, non-germline *BRCA* mut, all non-germline *BRCA* mut

Abbreviations: BID, twice daily; QD, daily; CYP, Cytochrome P450; SE, side effects; CMP, complete metabolic panel; CBC, complete blood count; BP, blood pressure; HR, heart rate; PS, platinum sensitive; PBC, platinum-based chemotherapy; HGS, high grade serous; EOC, epithelial ovarian cancer; HG, high grade; HRD, homologous recombination deficiency; mut, mutant.

definition of HRD, and amount of residual disease allowed. Furthermore, method of primary endpoint assessment differed between investigator assessment and BICR as well as radiographic scan intervals. Cost will likely be an important consideration in the future.

6.7. Combination therapy involving PARPi for platinum-sensitive recurrent EOC

Synergy between PARPi and chemotherapy is thought to occur due to the disruption of base excision repair by PARPi which is partly responsible for the repair of damage caused by cytotoxic chemotherapy. Although there is plausible rationale behind this combination strategy, achievement of full dose chemotherapy has been limited due to overlapping myelosuppressive toxicities.

Table 3
Adverse events of PARP inhibitors.

	Olaparib SOLO2 [49]		Rucaparib ARIEL3 [41]		Niraparib NOVA [54]	
	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)	Any Grade (%)	Grade 3/4 (%)
Blood disorders						
Anemia	24	19	37	19	50	25
Thrombocytopenia	13	1	18	5	61	34
Neutropenia	14	5	28`	7	30	20
GI disorders						
Nausea	73	3	75	4	74	3
Vomiting	35	3	37	4	34	2
Diarrhea	32	1	32	1	19	0.3
Constipation	21	0	37	2	40	0.5
Dyspepsia	11	0	15	<1%	11	0
General disorders						
Fatigue	62	4	69	7	59	8
Dysgeusia	27	0	39	0	10	0
Headache	25	1	18	<1	26	0.3
Insomnia	–	–	14	0	24	0.3
MSK disorders						
Arthralgia	15	0	15	1	11.7	0.3
Dose interruption	45		64		69	
Dose reduction	25		55		66	
Drug discontinued	11		13		14	
Any grade ≥ 3 AE	36		56		74	

Abbreviations: TCP, thrombocytopenia; GI, gastrointestinal; MSK, musculoskeletal; AE, adverse event.

Multiple phase I trials have evaluated PARPi with chemotherapy in solid tumors which have included EOC patients; however, the number of platinum-sensitive patients is not explicit [61–67]. Conducted as phase I trials in this patient population, veliparib (ABT888) has been studied in combination with topotecan, irinotecan, doxorubicin, cyclophosphamide, or gemcitabine and carboplatin [62–66]; rucaparib in combination with temozolomide, carboplatin, CP, and cisplatin and pemetrexed [67–69]. A phase II trial studied patients with platinum-sensitive recurrent EOC and demonstrated that olaparib plus CP resulted in an improved PFS when compared with chemotherapy alone. This is one of the first studies to demonstrate efficacy of combined PARPi and chemotherapy [70].

Studies have also investigated the potential synergy of PARPi with anti-angiogenic agents given preclinical data which suggest that PARPi sensitivity is enhanced in hypoxic states [71,72]. Based on compelling phase I/II data of olaparib with a cediranib, there is an ongoing NRG Oncology trial (NCT#02446600) evaluating platinum-based doublet chemotherapy versus olaparib monotherapy versus olaparib and cediranib in women with platinum-sensitive recurrent EOC [73]. A phase I/II AVANOVA (NCT02354131) is randomizing platinum-sensitive recurrent EOC patients to niraparib versus niraparib and bevacizumab and has demonstrated an overall response rate of 45% [74]. Phase II data has yet to be presented. Another phase I/II trial (NCT02953457) is studying olaparib with anti-programmed death 1 ligand (PD-L1) antibody durvalumab and anti-CTLA4 antibody tremelimumab in platinum-sensitive and resistant disease. Further development of these combinations are needed and have already expanded to include other immunotherapy agents and PI3-kinase inhibitors based on preclinical studies showing upregulation of PD-L1 expression and synergistic effects on delayed tumor doubling [75,76].

6.8. Short-term side effects of PARPi

Treatment with PARPi is overall well tolerated, but as expected, grade ≥ 3 adverse events are more common with maintenance treatment than with placebo. In the landmark studies, treatment interruption occurred in 45% of patients with olaparib and ~65% with niraparib and rucaparib (Table 3) [41,49,54]. However, treatment discontinuation of PARPi secondary to side effects occurred in only 10–15% of patients (Table 3).

The most common grade ≥ 3 side effects attributed to the class effects of these drugs include anemia, fatigue that can be offset with non-pharmacologic options or the use of methylphenidate, nausea

and vomiting which can be managed with a 5 HT3 antagonist initially and then adding other agents if necessary (Table 3) [32]. There are safety and toxicity differences between different PARPi which are noted in Table 3 and discussed under each PARPi section above. Dose interruptions and reductions are appropriate if patients are experiencing unacceptable side effects. Suggested dose reductions are noted in Table 3.

Despite these side effects, all studies to date evaluating QOL in patients taking PARPi compared to placebo or alternative treatments have demonstrated no difference in QOL [40,50,58]. In fact, it has even been suggested that PARPi may delay time to deterioration of QOL due to its therapeutic effects.

6.9. Long-term side effects of PARPi

The main adverse effects of PARPi and how to manage them are noted above. A concerning side effect to discuss is the possibility of a subsequent myelodysplastic syndrome (MDS) or AML due to the disruption of inherent DNA repair mechanisms. Early olaparib studies demonstrated an incidence of MDS/AML of <1.5% with the majority of these cases resulting in death leading to a formal FDA warning for PARPi [51]. However, multiple other studies have confirmed this risk is no higher than that experienced with placebo with an occurrence rate of 1–2% [41,49,54]. Further data is necessary to determine other long-term effects given the majority of studies occurred within the past 10 years and the exposure to these drugs continues to increase.

6.10. Future development of PARPi

Many important questions arise in response to PARPi treatment specifically regarding their utility as a first line maintenance therapy, a monotherapy, switch maintenance from a bevacizumab based regimen, and the effectiveness of "PARP-after-PARP" therapy.

Maintenance therapy with PARPi has shown promising results in treating all platinum-sensitive recurrent EOC patients regardless of *BRCA* or HRD abnormalities as discussed above. However, there is no reported data to suggest the efficacy of using PARPi as front-line maintenance treatment. The PRIMA trial for niraparib (NCT02655016) and SOLO1 trial for olaparib (NCT01844986) are phase III double-blind placebo-controlled RCTs evaluating maintenance after front-line platinum-based chemotherapy treatment in *BRCA* patients (SOLO1) and in all patients (PRIMA) with newly diagnosed stage III/IV EOC. A press release by olaparib's manufacturer states that SOLO1 met its primary endpoint of PFS, but data are yet to be presented [77]. Other current phase III RCT trials evaluating upfront maintenance include PAOLA-1 (NCT02477644) using olaparib maintenance therapy after upfront platinum therapy plus bevacizumab and GOG 3005 (NCT02470585) which is studying CP with or without concurrent and continuation maintenance veliparib in newly diagnosed stage III/IV HGSC patients.

Once these data mature and if results are promising, we may be faced with the practical dilemma of choosing between bevacizumab vs a PARPi for front-line maintenance treatment for women with advanced EOC. As it stands now, data from a secondary analysis of GOG218, suggests that patients with ascites treated with first-line CP + Bev have an improved PFS (adjusted HR 0.71, 95% CI 0.62–0.81, $p < 0.001$) and OS (adjusted HR 0.82, 95% CI 0.70–0.96, $p = 0.014$) when treated with CP + Bev compared to CP + placebo [78]. Other practical implications of using bevacizumab upfront for advanced stage EOC are cost-effectiveness and consideration that the AURELIA trial demonstrated that bevacizumab confers improved PFS in platinum-resistant recurrent EOC [79]. Without available trials comparing bevacizumab vs PARPi as front-line maintenance; or testing effectiveness of bevacizumab in the recurrent setting among women treated with first-line bevacizumab (only 7.2% had a prior anti-angiogenic therapy in AURELIA; and MITO-16 is ongoing), we are faced with a data-free zone.

Two current phase III trials are evaluating the effectiveness of PARPi as monotherapy for recurrent EOC. SOLO3 (NCT02282020) is comparing olaparib versus physician's choice of non-platinum chemotherapy. ARIEL4 is studying rucaparib versus chemotherapy. These trials are anticipated to be completed in 2019 (SOLO3) and 2022 (ARIEL4).

There is no data to date evaluating retreatment with a PARPi or the PARP-after-PARP strategy. Estimated to be completed in 2020, OReO/ENGOT (NCT03106987) is a phase III RCT of olaparib maintenance retreatment versus placebo in patients who have previously received a maintenance PARPi and have a CR or PR to recent platinum-based chemotherapy.

Other important objectives of future clinical research include investigating predictive markers of response, reasons for PARPi resistance, and how to enhance PARPi efficacy in combination with anti-angiogenic drugs and immunotherapy.

7. Conclusion

The majority of women with platinum-sensitive EOC will recur and given the ever-changing paradigm of upfront management, use of new targeted strategies based on the tumor biology will dictate which therapies we use in the recurrent setting. Although previous advances in disease management have resulted in prolonged OS, the mortality rates remain dismal. Fortunately, the arsenal of treatment options is rapidly expanding to include not only platinum-based chemotherapy but also molecularly targeted drugs which have and will continue to improve survival. Drug development and research to identify markers predictive of response must continue in order to optimize care of platinum-sensitive recurrent EOC.

Conflict of interest statement

The authors declare the following conflicts of interest: PHT has received fees for serving on advisory boards for Celsion, Tesaro, Clovis Oncology, Genentech, speaker fees from Tesaro and Merck, and institutional grant money from Merck.

Contributors

Premal Thaker oversaw this publication as well as participated in conception and design of the work, drafting the article, critical revision of the article, and final approval of the version to be published. Mary Mullen participated in drafting the article, critical revision of the article, and final approval of the version to be published. Lindsay Kuroki participated in drafting the article, critical revision of the article, and final approval of the version to be published.

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References

[1] L.A. Torre, B. Trabert, C.E. DeSantis, K.D. Miller, G. Samimi, C.D. Runowicz, et al., Ovarian Cancer Statistics, CA Cancer J. Clin. (2018) 2018.
[2] M.K. Parmar, J.A. Ledermann, N. Colombo, A. du Bois, J.F. Delaloye, G.B. Kristensen, et al., Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial, Lancet 361 (9375) (2003) 2099–2106.
[3] The International Collaborative Ovarian Neoplasm (ICON) Group, Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial, Lancet 360 (2002) 505–515.
[4] M.A. Bookman, M.F. Brady, W.P. McGuire, P.G. Harper, D.S. Alberts, M. Friedlander, et al., Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup, J. Clin. Oncol. 27 (9) (2009) 1419–1425.
[5] R.E. Bristow, R.S. Tomacruz, D.K. Armstrong, E.L. Trimble, F.J. Montz, Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis, J. Clin. Oncol. 20 (5) (2002) 1248–1259.
[6] M.K. Wilson, E. Pujade-Lauraine, D. Aoiki, M.R. Mirza, D. Lorusso, et al., Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease, Ann. Oncol. 28 (2017) 727–732.

[7] M. Friedlander, E. Trimble, A. Tinker, D. Alberts, E. Avall-Lundqvist, M. Brady, et al., Clinical trials in recurrent ovarian cancer, Int. J. Gynecol. Cancer 21 (4) (2011) 771–775.
[8] E.A. Eisenhauer, J.B. Vermorken, M. van Glabbeke, Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients [seecomments], Ann. Oncol. 8 (10) (1997) 963–968.
[9] R.E. Bristow, I. Puri, D.S. Chi, Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis, Gynecol. Oncol. 112 (1) (2009) 265–274.
[10] T. Al Rawahi, A.D. Lopes, R.E. Bristow, A. Bryant, A. Elattar, S. Chattopadhyay, et al., Surgical cytoreduction for recurrent epithelial ovarian cancer, Cochrane Database Syst. Rev. (2) (2013), Cd008765.
[11] A.D. Bois, I. Vergote, G. Ferron, A. Reuss, W. Meier, S. Greggi, et al., Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20, J. Clin. Oncol. 35 (15_suppl) (2017) 5501.
[12] R.L. Coleman, D. Enserro, N. Spirtos, T.J. Herzog, P. Sabbatini, D.K. Armstrong, et al., A phase III randomized controlled trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy (PBC), with or without bevacizumab (B) in platinum-sensitive, recurrent ovarian cancer (PSOC): a NRG Oncology/Gynecologic Oncology Group (GOG) study, J. Clin. Oncol. 36 (15_suppl) (2018) 5501.
[13] R. van de Laar, P.L. Zusterzeel, T. Van Gorp, M.R. Buist, W.J. van Driel, K.N. Gaarenstroom, et al., Cytoreductive surgery followed by chemotherapy versus chemotherapy alone for recurrent platinum-sensitive epithelial ovarian cancer (SOCceR trial): a multicenter randomised controlled study, BMC Cancer 14 (2014) 22.
[14] D. Luvero, A. Milani, J.A. Ledermann, Treatment options in recurrent ovarian cancer: latest evidence and clinical potential, Ther Adv Med Oncol. 6 (5) (2014) 229–239.
[15] J. Pfisterer, M. Plante, I. Vergote, A. du Bois, H. Hirte, A.J. Lacave, et al., Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG, J. Clin. Oncol. 24 (29) (2006) 4699–4707.
[16] E. Pujade-Lauraine, U. Wagner, E. Aavall-Lundqvist, V. Gebski, M. Heywood, P.A. Vasey, et al., Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse, J. Clin. Oncol. 28 (20) (2010) 3323–3329.
[17] U. Wagner, C. Marth, R. Largillier, J. Kaern, C. Brown, M. Heywood, et al., Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients, Br. J. Cancer 107 (4) (2012) 588–591.
[18] D. Koensgen, D. Stengel, A. Belau, P. Klare, G. Oskay-Oezcelik, T. Steck, et al., Topotecan and carboplatin in patients with platinum-sensitive recurrent ovarian cancer. Results of a multicenter NOGGO: phase I/II study, Cancer Chemother. Pharmacol. 62 (3) (2008) 393–400.
[19] F.A. Raja, N. Counsell, N. Colombo, J. Pfisterer, A. du Bois, M.K. Parmar, et al., Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data, Ann. Oncol. 24 (12) (2013) 3028–3034.
[20] M.E. Gore, I. Fryatt, E. Wiltshaw, T. Dawson, Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds, Gynecol. Oncol. 36 (2) (1990) 207–211.
[21] A. Poveda, I. Vergote, S. Tjulandin, B. Kong, M. Roy, S. Chan, et al., Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6–12 months) subpopulation of OVA-301 phase III randomized trial, Ann. Oncol. 22 (1) (2011) 39–48.
[22] S.B. Kaye, N. Colombo, B.J. Monk, S. Tjulandin, B. Kong, M. Roy, et al., Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer delays third-line chemotherapy and prolongs the platinum-free interval, Ann. Oncol. 22 (1) (2011) 49–58.
[23] S. Pignata, G. Scambia, A. Bologna, S. Signoriello, I.B. Vergote, U. Wagner, et al., Randomized controlled trial testing the efficacy of platinum-free interval prolongation in advanced ovarian cancer: the MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study, J. Clin. Oncol. 35 (29) (2017) 3347–3353.
[24] J. Schmitt, D. Matei, Targeting angiogenesis in ovarian cancer, Cancer Treat. Rev. 38 (4) (2012) 272–283.
[25] C. Aghajanian, S.V. Blank, B.A. Goff, P.L. Judson, M.G. Teneriello, A. Husain, et al., OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer, J. Clin. Oncol. 30 (17) (2012) 2039–2045.
[26] C. Aghajanian, B. Goff, L.R. Nycum, Y.V. Wang, A. Husain, S.V. Blank, Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer, Gynecol. Oncol. 139 (1) (2015) 10–16.
[27] S. Pignata, D. Lorusso, F. Joly, C. Gallo, N. Colombo, et al., Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: the randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17, Abstract ASCO 5506 (2018).
[28] J.A. Ledermann, A.C. Embleton, F. Raja, T.J. Perren, G.C. Jayson, G.J.S. Rustin, et al., Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial, Lancet 387 (10023) (2016) 1066–1074.
[29] J.A. Ledermann, A.C. Embleton, T. Perren, G.C. Jayson, G.J.S. Rustin, S.B. Kaye, et al., Overall survival results of ICON6: A trial of chemotherapy and cediranib in relapsed ovarian cancer, J. Clin. Oncol. 35 (15_suppl) (2017) 5506.
[30] D.P. Stark, A. Cook, J.M. Brown, M.D. Brundage, A.C. Embleton, R.S. Kaplan, et al., Quality of life with cediranib in relapsed ovarian cancer: the ICON6 phase 3 randomized clinical trial, Cancer 123 (14) (2017) 2752–2761.
[31] B.J. Monk, A. Poveda, I. Vergote, F. Raspagliesi, K. Fujiwara, D.S. Bae, et al., Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): long-term survival, impact of ascites, and progression-free survival-2, Gynecol. Oncol. 143 (1) (2016) 27–34.
[32] C.C. Gunderson, U. Matulonis, K.N. Moore, Management of the toxicities of common targeted therapeutics for gynecologic cancers, Gynecol. Oncol. 148 (3) (2018 Mar) 591–600.
[33] S.B. De Lorenzo, A.G. Patel, R.M. Hurley, S.H. Kaufmann, The elephant and the blind men: making sense of PARP inhibitors in homologous recombination deficient tumor cells, Front. Oncol. 3 (2013) 228.
[34] A.G. Patel, J.N. Sarkaria, S.H. Kaufmann, Nonhomologous end joining drives poly (ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells, Proc. Natl. Acad. Sci. U. S. A. 108 (8) (2011) 3406–3411.
[35] C.L. Scott, E.M. Swisher, S.H. Kaufmann, Poly (ADP-ribose) polymerase inhibitors: recent advances and future development, J. Clin. Oncol. 33 (12) (2015) 1397–1406.
[36] H. Farmer, N. McCabe, C.J. Lord, A.N. Tutt, D.A. Johnson, T.B. Richardson, et al., Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy, Nature 434 (7035) (2005) 917–921.
[37] J. Murai, S.Y. Huang, B.B. Das, A. Renaud, Y. Zhang, J.H. Doroshow, et al., Trapping of PARP1 and PARP2 by clinical PARP inhibitors, Cancer Res. 72 (21) (2012) 5588–5599.
[38] P.C. Fong, D.S. Boss, T.A. Yap, A. Tutt, P. Wu, M. Mergui-Roelvink, et al., Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers, N. Engl. J. Med. 361 (2) (2009) 123–134.
[39] K.A. Gelmon, M. Tischkowitz, H. Mackay, K. Swenerton, A. Robidoux, K. Tonkin, et al., Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study, Lancet Oncol. 12 (9) (2011) 852–861.
[40] J. Ledermann, P. Harter, C. Gourley, M. Friedlander, I. Vergote, G. Rustin, et al., Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial, Lancet Oncol. 15 (8) (2014) 852–861.
[41] R.L. Coleman, A.M. Oza, D. Lorusso, C. Aghajanian, A. Oaknin, A. Dean, et al., Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet 390 (10106) (2017) 1949–1961.
[42] K.P. Pennington, T. Walsh, M.I. Harrell, M.K. Lee, C.C. Pennil, M.H. Rendi, et al., Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas, Clin. Cancer Res. 20 (3) (2014) 764–775.
[43] Cancer Genome Atlas Research N, Integrated genomic analyses of ovarian carcinoma, Nature 474 (7353) (2011) 609–615.
[44] P.A. Konstantinopoulos, D. Spentzos, B.Y. Karlan, T. Taniguchi, E. Fountzilas, N. Francoeur, et al., Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer, J. Clin. Oncol. 28 (22) (2010) 3555–3561.
[45] J.I. Weberpals, K.V. Clark-Knowles, B.C. Vanderhyden, Sporadic epithelial ovarian cancer: clinical relevance of BRCA1 inhibition in the DNA damage and repair pathway, J. Clin. Oncol. 26 (19) (2008) 3259–3267.
[46] S.B. Kaye, J. Lubinski, U. Matulonis, J.E. Ang, C. Gourley, B.Y. Karlan, et al., Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer, J. Clin. Oncol. 30 (4) (2012) 372–379.
[47] J. Ledermann, P. Harter, C. Gourley, M. Friedlander, I. Vergote, G. Rustin, et al., Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer, N. Engl. J. Med. 366 (15) (2012) 1382–1392.
[48] J.A. Ledermann, P. Harter, C. Gourley, M. Friedlander, I. Vergote, G. Rustin, et al., Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial, Lancet Oncol. 17 (11) (2016) 1579–1589.
[49] E. Pujade-Lauraine, J.A. Ledermann, F. Selle, V. Gebski, R.T. Penson, A.M. Oza, et al., Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and BRCA 1/2 mutation (SOLO2/ENGOT-OV21): a double randomised, placebo-controlled, phase 3 trial, Lancet Oncol. 18 (9) (2017) 1274–1284.
[50] M. Friedlander, V. Gebski, E. Gibbs, L. Davies, R. Bloomfield, F. Hilpert, et al., Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial, Lancet Oncol. 19 (8) (2018) 1126–1134.
[51] FDA, Lynparza (olaparib) tablets, for oral use, Highlights of Prescribing Information, 2014.
[52] E.M. Swisher, K.K. Lin, A.M. Oza, C.L. Scott, H. Giordano, J. Sun, et al., Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 part 1): an international, multicentre, open-label, phase 2 trial, Lancet Oncol. 18 (1) (2017) 75–87.
[53] G.E. Konecny, A.M. Oza, A.V. Tinker, R.L. Coleman, D.M. O'Malley, L. Maloney, et al., Rucaparib in patients with relapsed, primary platinum-sensitive high-grade ovarian carcinoma with germline or somatic BRCA mutations: Integrated summary of efficacy and safety from the phase II study ARIEL2, Gynecol. Oncol. 145 (2) (2017).
[54] M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, et al., Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, N. Engl. J. Med. 375 (22) (2016) 2154–2164.

[55] FDA, Rubraca (rucaparib) tablets, for oral use, Highlights of Prescribing Information, 2016.
[56] FDA, Zejula (niraparib) capsules, for oral use, Highlights of prescribing information, 2017.
[57] S. Mahner, K. Moore, et al., ENGOT-OV16/NOVA: results of secondary efficacy endpoints of niraparib maintenance therapy in ovarian cancer, Paper presented at: The Society of Gynecologic Oncology Annual Meeting on Women's Cancer, National Harbor, Maryland, 2017 , (Seminal session 1 presentation).
[58] A.M.M.U. Oza, S. Malander, J. Sehouli, J.M. de Campo, et al., Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: results from the ENGOT-OV16/NOVA Trial, Annals of Oncology 28 (suppl_5) (2017) v330–v354, https://doi.org/10.1093/annonc/mdx372.
[59] U.A. Matulonis, J. Herrstedt, A. Tinker, F. Marme, A. Redondo, E. Kalbacher, et al., Long-term benefit of niraparib treatment of recurrent ovarian cancer (OC), J. Clin. Oncol. 35 (15_suppl) (2017) 5534.
[60] R.M.M. Lord, L. Woelber, et al., Safety and dose modification for patients with low body weight receiving niraparib in the ENGOT-OV16/NOVA phase III trial, Presented at: SGO Annual Meeting on Women's Cancer; March 24–27, 2018. New Orleans, 2018 , (Abstract 20).
[61] J.M. Lee, J.L. Hays, C.M. Annunziata, A.M. Noonan, L. Minasian, J.A. Zujewski, et al., Phase I/Ib study of olaparib and carboplatin in BRCA1 or BRCA2 mutation-associated breast or ovarian cancer with biomarker analyses, J. Natl. Cancer Inst. 106 (6) (2014), dju089.
[62] S. Kummar, A. Chen, J. Ji, Y. Zhang, J.M. Reid, M. Ames, et al., Phase I study of PARP inhibitor ABT-888 in combination with topotecan in adults with refractory solid tumors and lymphomas, Cancer Res. 71 (17) (2011) 5626–5634.
[63] S. Kummar, J. Ji, R. Morgan, H.J. Lenz, S.L. Puhalla, C.P. Belani, et al., A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas, Clin. Cancer Res. 18 (6) (2012) 1726–1734.
[64] P.J.J. Lorusso, J. Li, L.K. Heilbrun, G. Shapiro, E.A. Sausville, et al., Phase I study of the safety, pharmacokinetics and pharmacodynamics of the poly (ADP-ribose) polymerase (PARP) inhibitor veliparib (ABT-888) in combintion with irinotecan (CPT-111) in patients with advanced solid tumors, J. Clin. Oncol. 299 (Suppl.: abstract 3000) (2011) (2011).
[65] A.R.T.D. Tan, M.N. Stein, R.A. Moss, M. Gounder, D.C. Lindquist, et al., Phase I trial of veliparib (ABT-888): a poly (ADP-ribose) polymerase (PARP) inhibitor in combination with doxorubicin and cyclophosphamide in breast cancer and other solid tumors, J. Clin. Oncol. 29 (Suppl.: abstract 3041) (2011).
[66] H.J. Gray, K. Bell-McGuinn, G.F. Fleming, M. Cristea, H. Xiong, D. Sullivan, et al., Phase I combination study of the PARP inhibitor veliparib plus carboplatin and gemcitabine in patients with advanced ovarian cancer and other solid malignancies, Gynecol. Oncol. 148 (3) (2018) 507–514.
[67] R. Plummer, C. Jones, M. Middleton, R. Wilson, J. Evans, A. Olsen, et al., Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors, Clin. Cancer Res. 14 (23) (2008) 7917–7923.
[68] P.M.L. Roxburgh, A. Gupta, R. Wilson, J. Evans, N. Cresti, et al., A phase I study of oral rucaparib in combination with carboplatin, Proceedings from the European Cancer Congress, 2013 , (abstract 155).
[69] R.H. Wilson, T.J. Evans, M.R. Middleton, L.R. Molife, J. Spicer, V. Dieras, et al., A phase I study of intravenous and oral rucaparib in combination with chemotherapy in patients with advanced solid tumours, Br J Cancer. 116 (7) (2017) 884–892.
[70] A.M. Oza, D. Cibula, A.O. Benzaquen, C. Poole, R.H. Mathijssen, G.S. Sonke, et al., Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial, Lancet Oncol. 16 (1) (2015) 87–97.
[71] R.S. Bindra, S.L. Gibson, A. Meng, U. Westermark, M. Jasin, A.J. Pierce, et al., Hypoxia-induced down-regulation of BRCA1 expression by E2Fs, Cancer Res. 65 (24) (2005) 11597–11604.
[72] D.C. Hegan, Y. Lu, G.C. Stachelek, M.E. Crosby, R.S. Bindra, P.M. Glazer, Inhibition of poly(ADP-ribose) polymerase down-regulates BRCA1 and RAD51 in a pathway mediated by E2F4 and p130, Proc. Natl. Acad. Sci. U. S. A. 107 (5) (2010) 2201–2206.
[73] J.F. Liu, W.T. Barry, M. Birrer, J.M. Lee, R.J. Buckanovich, G.F. Fleming, et al., Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study, Lancet Oncol. 15 (11) (2014) 1207–1214.
[74] M.R. Mirza, J. Wang, M. Mau-Sørensen, M.J. Birrer, X. Wang, M. Jørgensen, et al., 953PA phase 1 study to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy and determine the recommended phase 2 dose (RP2D) in women with platinum-sensitive epithelial ovarian cancer (ENGOT-OV24/AVANOVA1), Ann. Oncol. 28 (suppl_5) (2017) (mdx372.024-mdx372.024).
[75] A. Juvekar, L.N. Burga, H. Hu, E.P. Lunsford, Y.H. Ibrahim, J. Balmana, et al., Combining a PI3K inhibitor with a PARP inhibitor provides an effective therapy for BRCA1-related breast cancer, Cancer Discov. 2 (11) (2012) 1048–1063.
[76] S. Jiao, W. Xia, H. Yamaguchi, Y. Wei, M.K. Chen, J.M. Hsu, et al., PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression, Clin. Cancer Res. 23 (14) (2017) 3711–3720.
[77] AstraZeneca, Lynparza significantly delays disease progression in Phase III 1st-line SOLO-1 trial for ovarian cancer, Press Release, 2018.
[78] J.S. Ferriss, J.J. Java, M.A. Bookman, G.F. Fleming, B.J. Monk, J.L. Walker, et al., Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG oncology/GOG study, Gynecol. Oncol. 139 (1) (2015) 17–22.
[79] E. Pujade-Lauraine, F. Hilpert, B. Weber, A. Reuss, A. Poveda, G. Kristensen, et al., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial, J. Clin. Oncol. 32 (13) (2014) 1302–1308.