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Review Article

Phase III trials in ovarian cancer: The evolving landscape of front line therapy

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HIGHLIGHTS

- There are many trials underway with biologic agents in combination and after primary chemotherapy for ovarian cancer.
- SOLO 1 has changed the standard primary therapy for women with BRCA mutated ovarian cancer.
- Other trials are likely to change the standard of care for the primary treatment of ovarian cancer.

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ABSTRACT

Introduction. Ovarian cancer has a high mortality to case ratio. To improve the initial response to therapy, trials of biologic agents in combination with primary chemotherapy and as maintenance after completing chemotherapy are being conducted. Multiple trials are ongoing and this strategy has great promise. However, the changing landscape of primary treatment will make designing future trials in ovarian cancer difficult as there may not be a consensus on the optimal primary therapy.

Materials and methods. We reviewed clinicaltrials.gov for recent and ongoing phase III clinical trials that are likely to impact primary therapy in ovarian cancer. We summarized the objectives and the available data from these trials.

Results. A total of 12 potentially practice-changing, randomized phase III trials in front line ovarian cancer were identified in which a biologic therapy was added to primary chemotherapy and/or was used in the maintenance setting. These trials included PARP inhibitors (PARPi), anti-angiogenic agents, immuno-oncology agents, and combinations of these agents. Of the 12 trials, 10 are ongoing, one was terminated for futility, and one has been recently reported. All of these trials emphasize the use of maintenance targeted therapy. In addition, 7 randomized phase III trials utilizing hyperthermic intraperitoneal chemotherapy (HIPEC) were identified in the setting of upfront ovarian cancer treatment.

Discussion. There are multiple ongoing trials in primary ovarian cancer. These trials investigate PARPi, anti-angiogenic agents, immuno-oncology agents, combinations of these agents, and HIPEC. Many of these trials will mature within the next several years and are likely to change the primary treatment of women with ovarian cancer.

Contents

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1. Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancy [1]. Although the mortality per case remains high, the median life expectancy of women with advanced ovarian cancer now approximates 5 years [2]. In the United States, over 220,000 women are ovarian cancer survivors. This represents a 20% increase between 2010 and 2015, and is due to a combination of improved surgery, supportive care, and the development of new chemotherapy drugs. Despite progress in treating recurrent ovarian cancer, little has changed in the primary treatment of ovarian cancer over the past 20 years.

Paclitaxel and cisplatin combination chemotherapy was introduced in 1996 as the standard of care for the treatment of patients with front line ovarian cancer [3]. This remained the standard of care until 2003, when a randomized trial of paclitaxel/carboplatin versus paclitaxel/cisplatin found paclitaxel/carboplatin to have similar efficacy, improved tolerability, and allowed outpatient administration [4]. Since that time, several randomized trials have been conducted including the use of prolonged maintenance chemotherapy, or the addition of additional cytotoxic agents [5] [6]. These trials have failed to demonstrate a significant improvement in outcome over every three-week carboplatin and paclitaxel. Other strategies that showed initial promise included dose-dense paclitaxel and intraperitoneal (IP) therapy [7,8]. While the initial trials were positive, confirmatory trials for both modalities failed to show benefit when compared to more modern chemotherapy regimens [9,10]. Given the lethality of advanced ovarian cancer and the lack of progress in advancing initial therapy for ovarian cancer, the need for innovative initial regimens is great.

Based on an increased understanding of ovarian cancer oncogenesis, proliferation, and metastasis, a number of targeted biologic agents have been incorporated into initial chemotherapy regimens and maintenance strategies. The number of current trials of new agents and combinations has led to a rapidly changing landscape in newly diagnosed ovarian cancer. While this variety offers great promise, the pace of change may complicate the design of future clinical trials in ovarian cancer while results of ongoing trials remain unavailable. Due to the number of ongoing and recently concluded studies, it is important to review the recent and future clinical trial portfolio in advanced ovarian cancer.

2. Materials and methods

To evaluate potentially practice-changing front line clinical trials in ovarian cancer, all phase III clinical trials involving patients with advanced ovarian cancer listed on cancer.gov were reviewed. Trials were identified in the database by searching for 'phase III' and 'ovarian cancer'. We included all trials that involved new biological agents in addition to chemotherapy in newly diagnosed high grade epithelial ovarian, fallopian, and peritoneal cancer which had not been completed as of 2018. Twelve potentially practice-changing randomized phase III trials of chemotherapy combined with biologic agents were identified (Table 1). Of these 12 trials, one has been reported, one was terminated for futility, five have completed enrollment, and five are enrolling patients. All of these trials emphasize maintenance therapy. In addition, 7 additional randomized phase III trials of HIPEC were identified. Additional information for the identified trials was obtained from clinical trial sites and from published reviews of these trials which are referenced in the respective sections. These data were abstracted and summarized.

3. Results

3.1. Anti-angiogenic agents

The use of anti-angiogenic therapy was explored in the front line setting in two randomized phase III trials, GOG 218 and ICON7 [11,12]. GOG 218 was a 3-arm, placebo-controlled, superiority trial that compared standard chemotherapy alone (Arm I) to standard chemotherapy plus bevacizumab starting at cycle 2 through cycle 6 (Arm II), or standard chemotherapy plus bevacizumab followed by maintenance bevacizumab from cycle 2 through cycle 22 with each cycle being 3 weeks in duration for a total of 15 months of bevacizumab (Arm III). The protocol initially enrolled only patients with residual disease >1 cm but was later amended to include patients with optimally resected, grossly visible disease after surgery. A total of 1873 women were recruited into this trial between October 2005 and June 2009. Arm III met the primary endpoint of prolonged PFS, including progression by CA-125 alone, with a hazard ratio (HR) of 0.72 (95% CI 0.63 to 0.82, $P < 0.001$). Overall, bevacizumab was well tolerated but was associated with hypertension requiring treatment in 22% of women on the maintenance arm. Gastrointestinal perforation and/or fistula formation was increased with bevacizumab treatment from 1.2% in the control arm to 2.6% in Arm III, although this difference was not statistically significant. Based on the positive results of this trial, bevacizumab was approved by the EMA. However, front line bevacizumab was not rapidly adopted in the United States. The reasons for this were multifactorial, but it was likely that the costs, potential side-effects, and need for 18 month of infusions did not justify the relatively small difference in median PFS between the control arm (Arm I) and the maintenance arm (Arm III) (10.3 vs 14.1 months) [13]. However, GOG 218 considered an increase in CA125 to be progression. The results of the trial were more striking in a planned sub-analysis in which patients who progressed only by CA125 were censored. This planned analysis yielded a HR for progression of 0.65 (95%CI 0.55–0.76, $P < 0.0001$) and a median increase in PFS from 12.0 to 18.0 months [11]. These data were submitted to the FDA and an approval was granted in June 2018 for a front-line indication in combination with primary chemotherapy and as maintenance in stage III/IV ovarian cancer after initial surgical resection [14].

ICON 7 had a trial design similar to GOG 218, but used a 50% lower dose of bevacizumab, was not placebo-controlled, and included only 12 months of bevacizumab in the maintenance arm [12]. Results were similar to GOG 218, as ICON 7 achieved the PFS endpoint with a hazard ratio (HR) for progression of 0.87 (95% CI 0.77–0.99, $P = 0.04$) resulting in a median PFS increase from 17.4 to 19.8 months. Similar to GOG 218, there was no reported increase in OS. In a preplanned sub-analysis of

Table 1
Overview of combination chemotherapy trials.

Trial	Size (randomization)	Status	Anti-angiogenic	PARPi	Immune	Start date	Est. primary completion
BOOST	800	Enrollment completed	Bevacizumab			Nov, 2011	Nov, 2018
SOLO-1	451(2:1)	Enrollment completed		Olaparib		Jan, 2012	Jul, 2018*
VELIA GOG-3005	1140	Enrollment completed		Velaparib		Jul, 2015	Apr, 2019
PRIMA ENGOT ov-26	620(2:1)	Enrollment completed		Niraparib		Apr, 2016	Feb, 2020
JAVLIN 100	998	Closed for futility			Avelumab	Mar, 2016	Dec, 2018
PAOLA-1 ENGOT-ov25	806(2:1)	Enrollment completed	Bevacizumab	Olaparib		Jul, 2015	Jun, 2022
IMaGYN050 GOG-3015 ENGOT Ov-39	1300	Enrollment complete	Bevacizumab		Atezolizumab	Mar, 2017	Apr, 2020
ATHENA GOG-3020 Engot-ov45	1012(1:1:4:4)	Enrolling		Rucaparib	Nivolumab	May 2018	Dec, 2024
JAVLIN 100 PARP	720	Enrolling	Bevacizumab	Talazoparib	Avelumab	Jul, 2018	Feb, 2022
FIRST Trial ENGOT Ov-44	960(1:1:2)	Enrolling	± Bevacizumab	Niraparib	Dostarlimab (TSR-042)	Oct, 2018	Nov, 2021
DUO-O ENGOT Ov-46	1056	Enrolling	Bevacizumab	Olaparib	Durvalumab	Dec, 2018	May 2022
ENGOT Ov-43 MK7339–001	1086	Enrolling	± Bevacizumab	Olaparib	Pembrolizumab	Dec, 2018	Aug, 2025

* Results announced

high risk patients with bulky >1 cm residual disease after resection or stage IV cancer, the PFS benefit was greater. In the sub-analysis of this group the median PFS increased from 10.5 to 16.0 months with a HR of 0.70 (95% CI 0.60 to 0.93, $P = 0.002$) [15]. A survival advantage was also noted in this high risk subgroup; the median OS increased from 28.8 to 36.6 months with a HR of 0.64 (95% CI 0.48 to 0.85, $P = 0.002$). A similar effect was noted among stage IV patients in GOG 218, as the OS increased from 32.6 to 42.8 months with a HR of 0.64 (95% CI 0.48 to 0.85, P = 0.002) [16]. It was noted that the stage IV patients on bevacizumab seemed to have an OS similar to the stage III patients [16]. Based on the data for benefit of bevacizumab in the front-line setting, the FDA granted approval for bevacizumab in front line ovarian cancer after surgery [14].

In both GOG 218 and ICON7, the reduction in the relative hazard for progression associated with bevacizumab administration appeared to be lost once maintenance bevacizumab therapy was stopped according to protocol. The BOOST trial (NCT01462890) will determine if prolonged bevacizumab could further improve PFS. In this trial, patients were randomized in a 1:1 fashion to a total of 15 months versus 30 months of bevacizumab. This trial enrolled 927 patients with stage III/IV high-grade ovarian cancer after primary surgical debulking. The first patient was enrolled in November 2011 and enrollment was completed in August 2013. The estimated date for the primary endpoint was November 2018 so results are expected soon [17]. The primary endpoint of this trial is PFS, and secondary endpoints include objective response rate, OS, quality of life (QOL), and safety.

3.2. PARP inhibitors

The poly-ADP ribose polymerase inhibitors (PARPi) rucaparib and olaparib were first approved in the treatment of patients with pathogenic mutations in *BRCA* [18,19]. PARPi have also been investigated as switch maintenance, in which a PARPi is introduced immediately after completion of chemotherapy. Currently, olaparib, niraparib, and rucaparib are approved for switch maintenance of patients with platinum-sensitive ovarian cancer who have responded to platinum in the second-line or third-line setting [18,20,21]. Based on the effectiveness of PARPi in the recurrent setting, there is interest in moving these drugs to the front line setting.

The SOLO-1 trial (NCT01844986) is an international superiority trial of maintenance olaparib in women with *BRCA* germ-line or somatic mutations after response to primary therapy with platinum-based chemotherapy [22]. This trial randomized 391 patients in a 2:1 fashion to olaparib 300 mg or placebo administered twice daily in tablet form. All patients had advanced disease, an attempt at cytoreductive surgery, and excellent performance status. Patients were stratified based on entry onto trial with a complete or partial response. Treatment was continued until disease progression or the completion of two years of therapy. If persistent disease remained and there was a perceived clinical benefit, therapy could be continued beyond two years. This occurred in 10% of patients on active drug and 2% of patients on placebo. Investigator assessed PFS was the primary endpoint, and secondary endpoints included OS and progression free survival 2 (PFS2) which is defined as the time from enrollment onto SOLO-1 until the time of second disease recurrence. Other secondary endpoints included time to first and second subsequent therapy (TFST, TSST), which is defined as the time of entry onto SOLO-1 until the first and second subsequent therapies are started, respectively, and QOL as measured by the health-related QOL trial outcome index (HRQoL TOI) scale and safety. With a median follow up of 41 months in each arm, SOLO-1 demonstrated that 24 months of maintenance olaparib reduced the risk of progression by 70% (HR = 0.30, 95% CI 0.23–0.41, $P < 0.001$) with a median increase in the PFS at 36 months (60% vs 27%) and an estimated improvement in PFS of 3 years compared to placebo. Further, there was no negative impact on subsequent lines of therapy as PFS2 remained statistically superior for the olaparib arm (HR = 0.50, 95% CI 0.35–0.72, P < 0.001). This is remarkable given that 35% of the patients who were initially on the placebo arm received a PARPi as maintenance after second line chemotherapy compared to only 11% of the patients in the olaparib arm. Olaparib maintenance was generally well tolerated with no new safety signals noted and no clinically relevant impact on QOL as measured by the HRQoL TOI [22]. The SOLO-1 trial led to an approval of olaparib as maintenance after primary chemotherapy [23].

There is an interest in combining PARPi with chemotherapy. In theory, PARP inhibition could potentiate chemotherapy by inhibiting sub-

lethal DNA repair in tumors. A phase I study showed that the PARPi veliparib could be combined with standard chemotherapy at a slightly reduced dosage [24]. Veliparib was then tested in a phase III setting in GOG 3005 (NCT02470585). This 3-arm placebo-controlled cooperative group trial randomized patients with stage III/IV ovarian cancer to carboplatin AUC 6 and paclitaxel (either 80 mg/m^2 per week or 175 mg/m^2 q 3 weeks) with placebo followed by 30 cycles (every 21 days) of oral placebo, chemotherapy plus veliparib followed by 30 cycles of placebo, or chemotherapy plus veliparib followed by 30 cycles of oral veliparib [25]. The study is fully enrolled and primary results are expected in 2019.

The PRIMA trial (NCT02655016) compares the use of niraparib maintenance for up to 3 years in patients who respond to primary chemotherapy regardless of *BRCA* status. This double-blind trial randomizes patients in a 2:1 fashion to niraparib 300 mg/day versus placebo in patients with serous or endometrioid stage IV ovarian cancer, or in stage III patients after NACT and interval debulking surgery, or with measurable disease after primary surgical debulking. Patients must have had a response to primary chemotherapy with normalization or >90% reduction in CA-125 levels, if initially elevated. Patients are stratified based on homologous recombination deficiency (HRD) status, use of neoadjuvant chemotherapy, and complete versus partial response to primary chemotherapy. In the non-germline *BRCA* cohort, PFS will be hierarchically evaluated first in HRD+ patients and, if significant, then in all non-germline *BRCA* patients. This study was opened in April 2016 and is fully enrolled [26]. The primary completion date for this study is estimated to be February 2020.

3.3. Immune checkpoint inhibitors

Single agent activity for PD-1 inhibition is low when considering all patients with ovarian cancer. However, response rates may be higher in women with *BRCA* mutations and other conditions which increase the neoantigen load [27,28]. Ovarian cancer does express neoantigens, and since many patients achieve a complete clinical response to primary chemotherapy, it is hoped that immunotherapy will prolong the disease free interval and OS if used in this setting [29]. While ovarian cancer is rarely microsatellite instability-high (MSI-H), pembrolizumab is currently approved for use in MSI-H ovarian cancer based on a tumor agnostic label for MSI-H cancers [30].

The JAVELIN trials test the addition of avelumab to chemotherapy for ovarian cancer. The first of these trials to be reported was JAVELIN 200 [31]. This trial enrolled 556 patients with platinum-resistant or platinum-refractory ovarian cancer. The study was a 3-arm randomized trial of pegylated liposomal doxorubicin (PLD) versus avelumab versus PLD with avelumab. The combination of PLD and avelumab had a response rate of 13.3% (95% CI 8.8%–19.0%) compared to 4.2% (95% CI 1.8%–8.1%) for PLD alone and 3.7% (95% CI 1.5%–7.5%) for single-agent avelumab. However, this trial did not meet the pre-specified PFS endpoint with a HR of 0.78 (95% CI 0.59–1.24) and a HR for OS of 0.89 (95%CI 0.74–1.24).

JAVELIN 100 (NTC02718417) is a Phase 3, open-label, international, multi-center, efficacy and safety study of avelumab in combination with and/or following platinum-based chemotherapy in previously untreated women with high grade epithelial, non-mucinous, stage III/IV ovarian cancer [32]. Patients could be enrolled with either primary debulking surgery or planned neoadjuvant chemotherapy with interval cytoreductive surgery. This three-arm trial is similar to previous trials where the arms include standard chemotherapy followed by a placebo, standard chemotherapy with avelumab, or standard chemotherapy with avelumab every 3 weeks followed by avelumab maintenance every 2 weeks for up to 2 years. The primary endpoint was PFS. The study commenced in May 2016 and enrolled at 998 patients. This study was closed prematurely for futility on 12/21/18 after planned interim analysis. Even though the trial is negative, it is hoped that translational endpoints may be able to identify a group that might benefit from this stategy.

3.4. Combination therapy

Many biologic agents do not have overlapping toxicities, and can be combined. There are theoretical advantages and experimental evidence to support the synergistic activity for combination biologic therapy. Several combinations are currently being tested, including PARPi with anti-angiogenics, PARPi with immune checkpoint inhibitors, immune checkpoint inhibitors with anti-angiogenics, and a combination of all three (Table 2).

Both bevacizumab and PARPi have demonstrated prolonged PFS in patients with recurrent platinum-sensitive ovarian cancer regardless of *BRCA* or HRD status [33–37]. A proposed mechanism of action for synergism of a combination of these two drugs involves hypoxia. Gene expression that controls HRD is suppressed in tumors that are hypoxic [38]. Bevacizumab induced hypoxia within tumors could be synergistic with PARP inhibition thereby producing a more lethal effect. Proof of principle for this concept has been demonstrated with the combination of the anti-VEGF tyrosine kinase inhibitor (TKI) cediranib with olaparib in the treatment of platinum-sensitive recurrent disease where the combination increased PFS from 9.0 to 17.7 months with a HR of 0.43 (95% CI 0.23–0.76, $P = 0.005$) [39]. The benefit of combination therapy was most pronounced in *BRCA wild-type* patients compared to *BRCA* mutated patients. In *BRCA wild-type* patients combination therapy improved median PFS from 5.7 to 16.5 months with a HR of 0.32 (95% CI 0.14–0.71, $p = 0.002$), compared to *BRCA* mutated patients, in whom combination therapy yielded no difference in median PFS when compared to olaparib alone; 16.5 versus 16.9 months with a HR of 0.75 (95% CI 0.38–1.49, $p = 0.16$). There are concerns with the toxicity associated with the TKI, and bevacizumab may be a more tolerable partner for PARPi, but efficacy of this combination is not yet demonstrated. Early studies suggest the combination of PARPi and bevacizumab is feasible with no unexpected toxicity in the maintenance setting [40]. The effects of angiogenic signaling are not limited to blood vessel growth, as anti-VEGF agents have demonstrated increased dendritic T-cell priming, depletion of regulatory T cells, and enhanced immune cell tumor infiltration [41–44]. Although other studies have suggested that immunosuppressive macrophages may be recruited to the microenvironment with anti-VEGF therapy, the combination of bevacizumab and immuno-oncology drugs may be synergistic.

Combining PARPi with immune checkpoint inhibitors may also be synergistic. A PARPi can increase DNA damage, lead to increased cytosolic DNA concentrations, and activate the STING pathway, thereby increasing tumor immunogenicity [45]. Clinical evidence also supports the synergy of this combination. KEYNOTE 162/TOPACIO (NTC02657889), a 62 patient phase I/II trial that combined niraparib with pembrolizumab in women with advanced platinum-resistant ovarian cancer, demonstrated a 25% to 30% response rate independent of *BRCA* mutational status or HRD classification [46].

3.5. Anti-angiogenic agents plus PARP Inhibitors

The PAOLA-1 or ENGOT-ov25 trial (NCT0247764) has enrolled 806 women in Europe and Japan with Stage IIIB to IV high grade ovarian cancer including serous, endometrioid, or other *BRCA*-mutated non-mucinous subtypes. All patients received platinum-based chemotherapy plus bevacizumab according to standard of care in many parts of Europe. Following complete or partial response to therapy, patients were continued on bevacizumab for 15 cycles and randomized to either olaparib or placebo for up to 24 months [47]. Patients were stratified based on *BRCA* status and response to primary chemotherapy. This trial was started in July 2015 and will be mature for the target PFS HR of 0.70 after 372 PFS events, which was estimated to occur in late 2018. The primary endpoint of this trial is PFS, and secondary endpoints

Table 2
Schema of new chemotherapy combination trials.

NCT number	Other names	Population	Agent with chemotherapy (paclitaxel + carboplatin)	Maintenance
NCT01462890	BOOST	Stage III/IV EOC allowed Neoadjuvant	Bevacizumab	Bevacizumab q 3 weeks x 15 months
			Bevacizumab	Bevacizumab q 3 weeks x 30 months
NCT01844986	SOLO-1	Stage III-IV serous CR or PR to primary chemotherapy BRCA mutated	None	Olaparib x 24 months
				Placebo x 24 months
NCT02470585	VELIA GOG3005	Stage III/IV EOC Serous Allows NACT	Placebo	Placebo x 24 months
			Velaparib	Placebo x 24 months
			Velaparib	Velapraib x 24 months
NCT02655016	PRIMA ENGOT ov-26	Stage III-IV macroscopic residual NACT allowed	None	Placebo x 36 months
				Niraparib x 36 months
NTC02718417	JAVLIN 100	Stage III residual Stage IV non-mucinous NACT allowed	Placebo	Placebo q 2 weeks x 24 months
			Placebo	Avelumab q 2 weeks x 24 months
			Avelumab q 3 weeks	Avelumab q 2 weeks x 24 months
NCT02477644	PAOLA-1 ENGOT-ov25	Stage IIB to IV Serous or Endometrioid or BRCA+	Bevacizumab (at least 2 cycles)	Bevacizumab q 3 weeks x 15 months
			Bevacizumab (at least 2 cycles)	Bevacizumab q 3 weeks x 15 months Olaparib x 24 months
NCT03038100	IMaGYN050 GOG3015 ENGOT Ov-39	Stage III-IV macroscopic residual NACT allowed	Bevacizumab	Bevacizumab x q 3 weeks + placebo q 3 weeks x 15 months
			Bevacizumab C2-6 Atezolizumab q 3 weeks	Bevacizumab q 3 weeks + Atezolizumab q 3 weeks x 15 months
NCT03522246	ATHENA GOG-3020 Engot-ov45	Stage III-IV Serous CR or PR with chemo NACT allowed	None	Placebo P + placebo IV q 4 weeks
				Placebo + IV nivolumab q 4 weeks
				Rucaparib po + IV placebo q 4 weeks
				Rucaparib po + IV nivolumab q 4 weeks
NCT03642132	JAVLIN 100 PARP	Stage III-IV Serous Macroscopic residual NACT allowed	Bevacizumab	Bevacizumab q 3 weeks until progression
			None	Talazoparib x until progression
			Avelumab	Avelumab q 2 weeks + talazoparib until progression
NCT03602859	FIRST Trial ENGOT Ov-44	Stage III-IV Stage IV and high risk stage III NACT allowed	± Bevacizumab + placebo IV	± Bevacizumab placebo IV + placebo PO
			± Bevacizumab + placebo IV	± Bevacizumab + placebo IV + niraparib PO
			± Bevacizumab dostarlimab (TSR-042) IV	IV dostarlimab (TSR-042) + niraparib PO
NCT03737643	DUO-O ENGOT Ov-46	Stage III-IV non-mucinous NACT allowed	Bevacizumab	Bevacizumab + IV placebo + placebo PO
			Bevacizumab + durvalumab	Bevacizumab + durvalumab IV+ placebo PO
			Bevacizumab + durvalumab	Bevacizumab + durvalumab IV + olaparib PO
NCT03740165	ENGOT Ov-43 MK7339-001	Stage III-IV non-mucinous NACT allowed low grade allowed	Placebo IV	Placebo IV + placebo PO x 24 months
			Pembrolizumab IV	Pembrolizumab IV + placebo PO x 24 months
			Pembrolizumab IV	Pembrolizumab IV + olaparib PO x 24 months

include PFS2, TFST, TSST, OS, safety, HRQOL, and patient reported outcomes (PROs).

3.6. Anti-angiogenic agents plus immune checkpoint inhibitors

The IMaGYN050 (NCT03038100) is a randomized blinded trial run by both GOG-Partners (GOG-3015) and ENGOT (ENGOT-Ov39). Patients with stage III/IV high grade epithelial ovarian cancer of all cell types are eligible. Patients with stage III disease must have macroscopic disease at the end of surgery or have received neoadjuvant chemotherapy (NACT). The neoadjuvant cohort is to be no >20% of the total enrollment. Standard doses of carboplatin and paclitaxel are given every three weeks with bevacizumab 15 mg/kg every 3 weeks from cycle 2 through cycle 22. Patients are randomized 1:1 to placebo or atezolizumab 1200 mg every 3 weeks for 22 cycles. Patients are stratified based on PD-L1 staining, stage, performance status, and use of NACT. This trial

has a co-primary endpoint of PFS and OS with a planned landmark analysis at 18 months. Secondary endpoints include RECIST defined PFS, progression based on CA125, OS, TFST, TSST, PRO and safety. This study will enroll approximately 1300 patients and was started in May 2017 and closed to enrollment in January 2019 [48]. Primary endpoint is estimated to be reached in April 2020.

3.7. PARPi plus immune checkpoint inhibitors

The ATHENA trial (NCT03522246) is a four-arm blinded randomized placebo-controlled trial that compares different combinations of maintenance therapy in patients with stage III/IV epithelial ovarian cancer who have responded to platinum-based therapy and had either primary surgery or NACT followed by interval cytoreductive surgery [49]. This trial is conducted by both the GOG Partners Foundation (GOG-3020) and ENGOT (ENGOT-ov45). The experimental maintenance arms include placebo, nivolumab IV every 4 weeks, rucaparib twice daily, or the combination of rucaparib and nivolumab. Randomization is in a 1:1:4:4 fashion. Nivolumab is discontinued after 24 months, but rucaparib continues as long as it is tolerated. The ATHENA trial started in May 2018 with a recruitment goal of approximately 1000 participants. The primary endpoint is PFS in molecularly defined HRD subgroups. Secondary endpoints include Blinded Independent Central Radiology Review (BICR)-assessed PFS, OS, ORR, duration of response (DOR), and toxicity. The primary study completion is estimated to be December 2024.

The JAVELIN 100 PARP trial (NCT03642132) is a three-arm trial in patients with newly diagnosed stage III/IV ovarian cancer after either primary debulking surgery or NACT [50]. Patients are required to have residual disease after primary debulking or planned NACT. The control arm includes upfront paclitaxel, carboplatin, and bevacizumab followed by bevacizumab maintenance therapy. The experimental arms are (1) chemotherapy and avelumab followed by avelumab and talazoparib maintenance, and (2) chemotherapy followed by talazoparib maintenance. The primary endpoint is PFS. All treatments are given until unacceptable toxicity or disease progression. This trial initiated in July 2018 with a planned enrollment of 720 women. The primary completion date is estimated to be February 2022. Because all experimental arms contain a PARPi, it is not expected that the premature closure of JAVELIN 100 will impact this trial.

The FIRST Trial (NCT03307785) is a randomized phase II/III trial for front line treatment of ovarian cancer combining niraparib and dostarlimab (TSR-042), an anti-PD-1 antibody, in the maintenance setting after response to platinum [51]. Bevacizumab is allowed but not required. This three-arm trial is conducted by ENGOT (ENGOT-Ov44) and will enroll approximately 960 patients with high risk stage III/IV disease with high-grade non-mucinous ovarian cancer. Patients with stage III disease are required to have NACT or bulky initial disease. The three arms include chemotherapy alone with or without bevacizumab followed by (1) placebo, (2) niraparib, or (3) niraparib plus dostarlimab (TSR-042) with maintenance therapy up to three years. Randomization is 1:1:2 and the patients are stratified by HRD status and the use of bevacizumab. The design is potentially adaptive based on results from other trials. For example, the arm containing only niraparib maintenance can be dropped in case the PRIMA or PAOLA trials are positive. The primary endpoint will be PFS with a target HR of approximately 0.70 for PFS at 90% power. Secondary endpoints are ORR, DOR, disease control rate (DCR), PROs, TFST, TSST, PFS2, and OS. This trial started in October 2018 with an estimated primary maturation in June 2020.

3.8. PARP inhibitors, checkpoint inhibitors, and anti-angiogenic agents

The DUO-O trial (ENGOT-ov46) is a randomized placebo controlled trial that will combine durvalumab (MEDI4736) with carboplatin, paclitaxel, and bevacizumab, followed by maintenance durvalumab, bevacizumab and olaparib [52]. Active agents in each arm include (Arm I) paclitaxel, carboplatin, and bevacizumab followed by maintenance bevacizumab, (Arm II) paclitaxel, carboplatin, bevacizumab, and durvalumab followed by maintenance bevacizumab and durvalumab, and (Arm III) paclitaxel, carboplatin, bevacizumab, and durvalumab followed by maintenance bevacizumab, durvalumab, and olaparib. Planned accrual is 927 patients, and this trial is slated to start in late 2018 and with an estimated completion date of May 2022.

Another randomized, placebo controlled, phase III trial in upfront ovarian cancer is ENGOT-ov43 [53]. This 3-armed trial combines paclitaxel and carboplatin with or without bevacizumab for 5 cycles followed by 30 cycles of (1) pembrolizumab and olaparib, (2) pembrolizumab and placebo, or (3) olaparib and placebo. Planned accrual is 1086 patients. This trial started in December, 2018 with an estimated primary completion date of August, 2025.

3.9. Intraperitoneal and hyperthermic intraperitoneal chemotherapy

Intraperitoneal (IP) therapy has shown a PFS and OS advantage in 3 trials. However, IP therapy was not popular due to toxicity and concurrent evolution of new chemotherapeutic agents. GOG 172 was a landmark IP trial published in 2006 [7]. GOG 172 met its primary endpoint of prolonging PFS from 18.3 to 23.8 months (HR = 0.80, $P = 0.03$). The median survival was not a primary endpoint but was noted to be increased from 49.7 months to 65.6 months (HR = 0.75, $P = 0.05$). In this trial, the IP arm contained 100 mg/m^2 of cisplatin compared to 75 mg/m^2 in the IV arm, resulting in considerably more grade 3/4 renal, toxicity, neurotoxicity, nausea, and emesis. Because of the toxicity of the high dose IP cisplatin, GOG 252 was designed as a three-arm trial with standard IV doses of carboplatin and paclitaxel compared with 75 mg/m^2 of IP cisplatin combined with IV and IP paclitaxel and a third arm of IP carboplatin at an AUC of 6 with IV paclitaxel [54]. All arms contained bevacizumab. Despite the three previous positive IP trials, GOG 252 failed to achieve the primary endpoint of an improvement in PFS. The survival data is not mature, but without a difference in PFS between the three arms it is doubtful that survival will be different. It is not known if the lack of benefit for IP therapy was due to the lower doses of IP cisplatin or the addition of bevacizumab. After this negative trial, enthusiasm for IP therapy has declined.

An exploratory analysis of GOG 172 revealed the PFS and OS benefits were limited to patients whose tumors had an abnormal *BRCA1* stain by IHC [55]. Other data suggest that patients with a pathogenic *BRCA* mutation appear to have a significant improvement in outcome with IP therapy, with a benefit from this modality much greater than that seen when comparing groups treated with IV therapy [56]. This indicates that BRCA (+) patients may be a group where IP therapy is of greater benefit.

A renewed interest has developed in Heated Intra-Peritoneal Chemotherapy (HIPEC) after a randomized trial showed a benefit in patients who received neoadjuvant chemotherapy followed by interval cytoreductive surgery and intra-operative HIPEC therapy [57]. This trial randomized 145 patients who had optimal resection at the time of interval cytoreductive surgery to HIPEC versus completion of standard therapy. The primary endpoint of this trial was PFS, which was met with a HR of 0.66 (95% CI 0.50 to 0.87, $P = 0.003$). The median recurrence free survival was 10.7 months in the surgery group and 14.2 months in the HIPEC group. The OS was also improved in the HIPEC group from 33.9 months to 45.7 months. However, the PFS improvement seen is similar to that observed with high-dose IP therapy and the addition of bevacizumab to primary chemotherapy. With substantial interest in maintenance therapy, the role of HIPEC in primary treatment of ovarian cancer remains unknown. This will become more well defined, as there are several phase III trials of HIPEC in women with newly diagnosed ovarian cancer that are ongoing (Table 3), and these trials may also identify subpopulations that are good candidates for HIPEC.

Table 3
Ongoing trials of HIPEC in primary ovarian cancer.

NCT number	Title	Other names	Status	Size	Country	Primary outcome	Start date	Est. primary completion
NCT02681432	Hyperthermic Intraperitoneal Chemotherapy with Paclitaxel in Advanced Ovarian Cancer	HIPECOVA HGCRCIRU001	Recruiting	60	Spain	OS	Jan, 2012	Sep, 2019
NCT01091636	Intraoperative Hyperthermic Intraperitoneal chemotherapy with Ovarian Cancer	NCCCTS-06-222	Unknown	170	Korea	PFS	Mar, 2010	Feb, 2016
NCT03373058	Efficacy of HIPC in the Treatment of Advanced-Stage Epithelial Ovarian Cancer after Cytoreductive Surgery	EHTASEOCCS HIPEC-04	Not yet recruiting	214	China	PFS	Mar, 2018	Jul, 2021
NCT03180177	Efficacy of HIPEC as NACT and Postoperative Chemotherapy in the Treatment of Advanced Stage Epithelial Ovarian Cancer	EHNPCTASEOC HIPEC-03	Not yet recruiting	263	China	PFS Rate of optimal resection Rate of non-progression at 1 year	Mar, 2018	Jul, 2021
NCT03371693	Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Lobaplatin in Advanced and Recurrent Epithelial Ovarian Cancer	HIPECOV	Active, not recruiting	222	China	OS 1 year landmark OS 3 year landmark OS	Sep, 2017	Dec, 2019
NCT01628380	Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer	CHORINE	Unknown	94	Germany/Italy	PFS	Jun, 2012	Jun, 2018
NCT02328716	Cytoreduction with or without Intraoperative Intraperitoneal Hyperthermic Chemotherapy (HIPEC) in Patients with Peritoneal Carcinomatosis from Ovarian Cancer, Fallopian Tube, or Primary Peritoneal Carcinoma	CARCINOHIPEC EC-GC/AD-01/11	Recruiting	32	Spain	PFS	Feb, 2012	Dec, 2018

4. Conclusions

There are many primary chemotherapy trials in patients with ovarian cancer and it is likely that at least some of these trials will be positive. It is hoped that these trials will lead to substantially improved PFS and OS and induce more long-term remissions or cures. However, until these trials mature, the standard of care for the primary treatment of ovarian cancer will remain uncertain. This may create a situation where there is no single standard of care for upfront ovarian cancer treatment, complicating future ovarian cancer trial design in both primary and recurrent settings. Adaptive trial designs may be the solution to this problem. As trials mature, multi-arm studies will need to modify enrollment criteria or drop an ineffective arm. The FIRST trial has already taken this into consideration, and arms will be modified as new data emerge. Based on the SOLO-1 data, patients that are BRCA mutated will no longer be randomized to the placebo arm, but will still be enrolled on the niraparib or niraparib plus dostarlimab (TSR-042) arms. Similar adjustments are planed if the results of the PRIMA and PAOLA trials are positive.

Some predictions can be made given the data that is available. For bevacizumab in the initial setting, there was a significant reduction in the HR for progression based on GOG 218 leading to an approval in the front-line setting in patients with high risk stage III and stage IV ovarian cancer [13]. This benefit appears to lessen when the drug is withdrawn. Therefore, it is likely that the BOOST trial will show a PFS benefit to continuation of bevacizumab. It is the magnitude of this effect that will determine if a prolonged course for maintenance is incorporated into the standard of care. Regardless of the duration of bevacizumab treatment in the initial setting, it is unlikely that this will influence trials in recurrent ovarian cancer. GOG-213 did not exclude patients with previous bevacizumab treatment and use of bevacizumab in the primary setting does not seem to impact the benefit to bevacizumab in the recurrent setting in an adhoc sub-analysis [36]. ENGOT-ov17 was specifically designed to answer the question of the effectiveness of continuing bevacizumab after progressing on a bevacizumab based chemotherapy regimen. This trial demonstrated continued benefit of bevacizumab with chemotherapy in ovarian cancer even if progression occurred on a chemotherapy regimen that included bevacizumab [58].

In the SOLO-1 trial, it was noted that the PFS was greatly extended after primary therapy with the use of a PARPi in patients with a *BRCA* mutation [22]. It is interesting that the HR for PFS in the SOLO-1 and SOLO-2 trials were identical with a 70% decrease in the risk of progression in both the initial maintenance setting and the switch maintenance setting in recurrent platinum-sensitive ovarian cancer. Currently, GOG-3005 and PRIMA are testing the concept of PARPi maintenance in both an HRD sub-population and in all patients with ovarian cancer. If the HRs in the primary setting are the same as in the recurrent setting, it is likely that PARPi after primary chemotherapy will become standard of care since these drugs were well tolerated in the SOLO-1 trial and it did not appear that early use of these agents decreased the efficacy of subsequent therapy. If PARPi maintenance after primary therapy becomes the standard of care for all patients, a significant question will arise concerning reintroduction of PARPi switch maintenance in the recurrent setting. Currently, the OReO trial is testing this concept for patients who fail a PARPi but subsequently respond to additional treatment. However, the situation for BRCA (+) patients treated in SOLO-1 is slightly different. BRCA (+) patients will have tumors that are more likely sensitive to PARPi. Because the duration for maintenance in SOLO-1 was only for 2 years, the majority of patients will progress after discontinuing the PARPi. It is likely that these patients with platinum sensitive recurrent ovarian cancer will still benefit from

PARPi switch maintenance even if previously treated with PARPi in the primary maintenance setting, even if the OReO trial is negative. However, this question will need to be tested.

At this time, it is difficult to predict the benefit to adding immunotherapy to front line regimens. While the data suggest synergy of immunotherapy with other biologic therapy, the overall response rate to these agents in ovarian cancer has not been impressive. The failure of the JAVELIN 100 trial in primary ovarian cancer would suggest that treating all patients with immunotherapy is likely not a practical approach. However, patients who do benefit from immunotherapy have the potential for long lasting effects. There may be subpopulations where these drugs are more effective, including patients with *BRCA* mutationed tumors, HRD, or other situations with a high mutational load or the increased tumor immunogenicity and combinations may show syntergy.

Ongoing trials in ovarian cancer certainly show great promise and we eagerly await the results of these studies. New therapies will likely increase the PFS for patients after initial therapy and have the potential to increase the permanent remission rates for patients with advanced disease. These data will undoubtedly result in an uncertainty about primary and future treatment as well as future trial design in both the primary and recurrent setting.

Conflict of interest statement

Dr. Naumann has received consulting fees from Genetech, Astra-Zeneca, Clovis, SutroBio, Merck, OncoMed, Janssen, and Tesaro; research funding from Bristol-Myers-Squib, OncoMed, and Merck; speaker fees from Genetech.

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Author contribution

Dr. Naumann generated the concept for this article was involved in data abstraction, writing, revision, and approval of the final manuscript.

Dr. Coleman was involved in writing, revision, and approval of the final manuscript.

Dr. Brown was involved in writing, revision, and approval of the final manuscript.

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