

## REVIEW ARTICLE

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# Is there a current change of maintenance treatment in ovarian cancer? An updated review of the literature

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## Summary

*Maintenance therapy in ovarian cancer has been introduced and evaluated in many large randomized trials; however, its efficacy is still unclear and includes concerns for both short-term and longer-term side effects. Thus far, some therapies that have been studied in this setting showed a delay in tumor progression but unfortunately no improvement in overall survival has been noticed. The introduction of new chemotherapeutic agents redirected research efforts. Assessing benefits of prolonged therapy and its impact in*

*terms of toxicity is considerably important for the decision to administer such treatments. The purpose of this article was to provide an update on the randomized trials and review the role of maintenance therapy in the treatment of ovarian cancer.*

**Key words:** chemotherapy, maintenance therapy, ovarian cancer

## Introduction

Fifty-70% of patients with epithelial ovarian cancer (EOC) who underwent optimal or suboptimal surgery achieve complete clinical remission with first-line chemotherapy (CT); however, 75% of them will experience disease recurrence within a median time of 18 to 28 months [1,2]. Despite all the years of research, the number of deaths due to high relapse rates after standard front-line treatment for advanced-stage disease could not be reduced. Even with effective second-line treatments, response rates decrease with each subsequent recurrence and 5-year survival for women with advanced-stage disease is only 30% [3,4]. Therefore, these unfavorable outcomes indicate the need for alternative schedules and have prompted researchers to search for maintenance treatments that might prolong a previously achieved response and reduce relapse rates.

Maintenance treatment means a prolonged

administration of chemotherapeutic agents with lower toxicity profiles to prevent recurrence in patients who had complete clinical remission with first-line CT. Alternative manipulations of the dosing schedule, dosage and agents have been suggested as a method of maintenance treatment of ovarian cancer and investigated in randomized trials. Low-dose CT following 6 cycles of the primary CT, short-term high-dose CT strategies, therapeutic vaccinations, immunological agents, intraperitoneal therapy (alone or combined with intravenous therapy) and targeted therapy have been investigated as maintenance therapy [5-8]. However, ideal chemotherapeutic agents, dosage, treatment interval and duration of maintenance treatment remain unclear and are being investigated. In this review, we aimed to provide an update on the accessible data and review the role of maintenance therapy in the treatment of ovarian cancer.

## Does platinum-taxane maintenance therapy contribute to survival advantage?

Platinum derivatives and taxanes which are the most effective agents for primary treatment have been used for maintenance treatment as a first choice. Several authors administered 3-6 doses of platinum+paclitaxel, or carboplatin, cisplatin or paclitaxel as single agents or intraperitoneal cisplatin following primary treatment as maintenance therapy for EOC, but most of the studies revealed no survival advantage [9,10]. In a meta-analysis by Mei et al. in which 6 randomized trials were included (N=902) maintenance CT with no further intervention, maintenance radiotherapy or other maintenance therapies were compared. No significant difference in 3-, 5- and 10-year overall survival (OS) or progression-free survival (PFS) was observed [11]. In 2013, this review was updated and analysed 8 trials (1644 women) including 3 studies comparing intravenous or intraperitoneal cisplatin, alone or combined with other drugs; 2 studies used paclitaxel. The studies revealed that none of the therapies improved survival rates. When all CT regimens were combined, meta-analysis indicated no significant difference in 3-, 5- and 10-year OS or PFS [2].

In GOG 178 trial, different numbers of paclitaxel courses were compared with each other. This was a phase 3 trial conducted by the Southwest Oncology Group (SWOG) and the Gynecologic Oncology Group (GOG) which included 277 patients (262 evaluable) with stage III disease who had achieved complete clinical remission. The study compared 3 cycles to 12 cycles of single-agent paclitaxel (175 mg/m<sup>2</sup> once a month) as a maintenance therapy after a primary platinum/paclitaxel CT program. A significant increase in PFS was observed in the 12-cycle group when compared with the 3-cycle group (7-month difference in median PFS, 28 vs 21 months, p=0.0023). However, improvement in survival led to increased rate of treatment-induced neuropathy (0.7% of the observation group compared to 4.4% of the maintenance paclitaxel group (p=0.012)) [12]. This was the only study that made comparison between intervention and control groups for toxicity. Infection, fever and dermatologic events were significantly higher among patients treated on the monthly maintenance paclitaxel (p<0.001). Furthermore, at the time the study was closed, this regimen showed no statistically significant benefit for OS [12,13].

GOG 212, an ongoing trial in which patients

with advanced EOC, who achieve a complete clinical response with primary platinum/taxane CT, are randomized into monthly paclitaxel, paclitaxel+polyglumex (Xyotax-CT-2103) or control groups after primary treatment for 12 months is being conducted. The primary endpoint of the study is OS while PFS and toxicities are secondary endpoints. GOG 212 also includes assessment of quality of life (QoL) as a secondary endpoint. This study may explain the role of paclitaxel in maintenance treatment and the results are awaited with interest [14].

## Other cytotoxic agents as maintenance therapy

Chemotherapeutics like topotecan, doxorubicin/epidoxorubicin, pegylated liposomal doxorubicin (PLD), 5-fluorouracil (5-Fu) and altretamine have been investigated as maintenance treatment [2,15-18].

The Multicenter Italian Trial in Ovarian Cancer (MITO-1) is a multicentric phase 3 randomized study to investigate whether topotecan (1.5 mg/m<sup>2</sup> on days 1 through 5, 4 cycles, every 3 weeks) prolonged PFS for patients responding to standard carboplatin and paclitaxel therapy. The analysis revealed with no significant improvement of median PFS (18.2 months in the topotecan arm and 28.4 in the control arm) in patients with advanced-stage EOC who responded to initial CT with carboplatin and paclitaxel. Besides, neutropenia (grade 3/4 in 58% of the patients) and thrombocytopenia (grade 3 in 21%; grade 4 in 3%) were the most frequent toxicities attributed to topotecan therapy [15].

A Gynecologic Cancer Intergroup trial of the AGO-OVAR and GINECO randomized a total of 1308 patients with previously untreated ovarian cancer (stage IIB-IV) to receive 6 cycles of paclitaxel and carboplatin followed by either 4 cycles of topotecan on a 3-week per cycle schedule or surveillance. The addition of topotecan did not result in superior PFS or OS. Compared with patients in the surveillance arm, patients in the topotecan arm had more grade 3-4 hematologic toxic effects (requiring more supportive care) and more grade 3-4 infections but did not have a statistically significant increase in febrile neutropenia [16].

Another multicentric randomized trial using epidoxorubicin as maintenance therapy reported no significant improvement in survival outcomes but a higher bone marrow toxicity profile attributed to the maintenance therapy [17].

The current data show no significant evidence

supporting the use of these cytotoxic agents as maintenance therapy for ovarian cancer.

### **Can immunological agents or vaccination create an immune response and used as maintenance therapy?**

Biological agents like oregovomab, tanomastat and IFN- $\alpha$  have been tried as maintenance treatment but unfortunately randomized phase 3 trials showed no evidence of improvement in survival rates [5-7,19].

The MIMOSA trial (Monoclonal antibody Immunotherapy for Malignancies of Ovary by Subcutaneous Abagovomab) is a phase 3 trial of vaccination by abagovomab (an antibody which functionally mimics the CA125 antigen). The trial involved repeat vaccinations every 4 weeks for up to 4 years or until disease recurrence in patients with complete clinical response to front-line treatment. Administration of abagovomab as maintenance therapy for patients with ovarian cancer in first remission resulted in no significant difference in PFS or OS [20].

### **Can targeted therapy lead to improved maintenance therapy in ovarian cancer?**

A possible role of antiangiogenic agents has been evaluated as a maintenance strategy of both the first-line and second-line management of EOC since they are one of the most promising approaches in cancer therapy [21]. Bevacizumab, the humanized monoclonal antibody that binds to VEGF-A, is the first angiogenesis inhibitor to have shown a significant PFS advantage in phase 3 trials and is arguably the standard of care for selected patients in the management of ovarian cancer [22]. Two comprehensive front-line phase 3 trials of bevacizumab in patients with EOC, GOG-218 and the International Collaboration on Ovarian Neoplasms (ICON)-7, reported that the addition of bevacizumab to the first-line carboplatin-taxane therapy followed by bevacizumab maintenance therapy, significantly improved PFS in 2011.

GOG-218 was a double-blinded, placebo-controlled phase 3 study enrolling 1873 women with untreated stage III or IV EOC [23]. After surgical cytoreduction, patients were randomly assigned to CT alone, CT plus concurrent bevacizumab or CT plus concurrent bevacizumab (15 mg/kg) followed by maintenance bevacizumab. Median PFS was 10.3 months in the control group, 11.2

months in the bevacizumab-initiation group, and 14.1 months in the bevacizumab-throughout group. The hazard of progression or death was significantly lower in the bevacizumab-throughout group compared with the control group ( $p < 0.001$ ) [23,24]. Similarly, ICON-7 was a phase 3 placebo-controlled randomized trial, enrolling 1528 women previously untreated with high risk, early-stage disease or advanced EOC [25]. Post-operatively, the patients were randomized to CT alone or CT with concurrent bevacizumab, followed by 12 cycles of maintenance bevacizumab or until disease progression. ICON-7 used lower dose of bevacizumab compared with GOG-218 trial (7.5 mg/kg every 21 days). In updated analyses, PFS at 42 months of follow-up improved from 22.4 months to 24.1 months with the addition of bevacizumab ( $p=0.04$ ) [24]. Furthermore, an OS advantage of 4.8 months (mean 34.5 vs 39.3 months;  $p=0.03$ ) in the bevacizumab arm for the subgroup of patients with a poor prognosis (FIGO stage III-IV disease or  $>1.0$  cm residual disease after debulking surgery) was obtained [26]. In both studies bevacizumab contributed to remarkable PFS advantage. The results of these two studies led to the approval of bevacizumab in the first-line treatment of ovarian cancer by the European Medicines Agency (EMA). However, it should be noted that details for OS of these studies are still immature and no significant improvement in OS has been reported yet. There is still not a consensus about bevacizumab as a standard first-line+maintenance therapeutic agent [26,27]. When considering the toxicity profile in both GOG-218 and ICON-7 trials, grade  $\geq 2$  hypertension was significantly more common in patients in the bevacizumab-containing arms. Fatal adverse events were reported in 1.0, 1.6 and 2.3% of patients in the control group, bevacizumab initiation group and bevacizumab maintenance group respectively in the GOG-218 trial and 0.1 and 0.5% in the CT arm and in the bevacizumab arm respectively in the ICON-7 trial [22-25].

As it is known the prognosis of recurrent ovarian cancer is determined by the time to progression from the last platinum-based treatment. Patients with a platinum-free interval of more than 6 months (platinum-sensitive disease) are likely to benefit from further therapy [28].

Bevacizumab is also being investigated as maintenance therapy after complete response to second-line treatment. In the platinum-sensitive recurrent disease trial Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive

Recurrent Disease (OCEANS), 484 patients whose disease had recurred  $\geq 6$  months after front-line platinum-containing CT were randomized to receive carboplatin+gemcitabine plus bevacizumab or carboplatin+gemcitabine plus placebo until evidence of disease progression [29]. Median PFS in the bevacizumab arm was superior to that in the placebo arm (12.4 months vs 8.4 months,  $p < 0.0001$ ) and the PFS advantage was maintained regardless of age, performance status, time to recurrence, and cytoreductive status. Overall response rate was significantly improved with the addition of bevacizumab (78.5 vs 57.4%,  $p < 0.0001$ ). However, there was no evidence of improved OS in relation with bevacizumab maintenance therapy. Grade 3 or higher hypertension (17.4 vs 1%) and proteinuria (8.5 vs 1%) were more frequent in the bevacizumab arm as expected. Two patients in the bevacizumab arm experienced gastrointestinal perforation. Other adverse events were similar in both arms [29]. EMA has approved bevacizumab in combination with carboplatin-gemcitabine in patients with first recurrence of platinum-sensitive EOC who have not received prior therapy with angiogenesis inhibitors.

Bevacizumab was also investigated in heavily pretreated platinum-resistant EOC populations. AURELIA is a randomized, phase 3 study that included 361 women with platinum-resistant or recurrent EOC, who had received a maximum 2 anticancer regimens prior to enrollment in the trial [30]. Patients were randomized to 6 treatment arms (paclitaxel, topotecan or pegylated liposomal doxorubicin with or without bevacizumab until disease progression). The study demonstrated a statistically significant improvement in PFS (6.7 vs 3.4 months) in the bevacizumab plus CT group compared with the CT alone group in platinum-resistant ovarian cancer. No difference in OS was observed between the treatment groups at the final data analysis [30,31]. Based on the results of this study, Food and Drug Administration (FDA) approved bevacizumab in combination with CT for the treatment of women with platinum-resistant or recurrent ovarian cancer. Adverse events were consistent with those seen in previous trials of bevacizumab including high blood pressure and pain. Bevacizumab-related gastrointestinal perforations were minimized in the AURELIA study due to the strict inclusion criteria [31].

The phase 3 randomized clinical trials including bevacizumab as a maintenance agent are summarized in Table 1.

GOG 213 is an ongoing phase 3 randomized

controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent EOC. The results of GOG 213 study are awaited with considerable interest for bevacizumab therapy and maintenance approach in platinum-sensitive recurrent ovarian cancer [32].

The role of another angiogenesis inhibitor, pazopanib, in maintenance treatment (an oral tyrosine-kinase inhibitor against vascular endothelial growth factor receptor (VEGF-R), platelet derived growth factor receptor (PDGF-R) and c-kit receptor) was investigated by Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR 16). It is a phase 3 study to evaluate the efficacy and safety of pazopanib monotherapy vs placebo in women who have not progressed after first line CT for EOC. According to the outcomes that were presented in 2013 American Society of Clinical Oncology Annual Meeting, maintenance treatment with pazopanib (800 mg/day) increased PFS rates of 900 patients who had completed their first-line treatment (median 17.9 vs 12.3 months, respectively,  $p = 0.0021$ ) [33]. An interim analysis showed no OS improvement. However, an increase of complications like grade 2 or greater hypertension (52 vs 17%), grade 3 or 4 diarrhea (8 vs 1%) and grade 3 or 4 hepatotoxicity (9 vs 1%) was observed during pazopanib treatment [33,34]. Unlike other bevacizumab studies, AGO-OVAR 16 was important for being the first prospective study that evaluated angiogenesis inhibitors as maintenance treatment following first-line CT as a single agent. It is promising because of the results for PFS.

Nintedanib (BIBF 1120) is a novel oral antiangiogenic agent, which works by simultaneously inhibiting VEGFR, as well as PDGF and FGF receptors. The LUME-Ovar-1 trial (also known as AGO-OVAR 12) randomized 1,366 patients with stage IIB-IV ovarian cancer after initial debulking surgery into BIBF 1120 in combination with standard treatment with carboplatin and paclitaxel or placebo plus carboplatin and paclitaxel until evidence of progression. Preliminary results were presented at the ESGO (European Society of Gynaecological Oncology) 2013 Conference, asserting that nintedanib significantly increased PFS in women with advanced ovarian cancer at the expense of more gastrointestinal adverse events. OS data are still immature [35].

Trebananib (AMG 386) is an angiopoietin (Ang) 1 and 2 neutralizing peptibody, with poten-

tial antiangiogenic activity. TRINOVA-3 is a phase 3 placebo-controlled ongoing trial of AMG 386 with paclitaxel and carboplatin as first-line treatment of subjects with FIGO stage III-IV epithelial ovarian, primary peritoneal or fallopian tube cancers. Patients were randomized to paclitaxel-carboplatin with placebo or trebananib followed by a maintenance period of trebananib/ placebo until the completion of 18 months if no evidence of

progression is detected [36].

Erlotinib, a tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR), was tested for maintenance treatment following primary CT. The results showed failure in improving PFS compared to placebo in a phase 3 randomized trial [37]. In addition, sorafenib, a multikinase inhibitor examined in a randomized phase 2 trial as maintenance therapy in patients with epithelial

**Table 1.** Bevacizumab as a maintenance agent included in 4 randomized clinical trials

Trial	Study design	Treatment arms	Median PFS (months)	Median OS (months)	Toxicity Thromboelism (venous+arterial) %	Hypertension (grade $\geq 2$ ) %	Proteinuria (grade $\geq 3$ ) %	GI (grade $\geq 2$ ) %
GOG-218 [24] (n=1,873)	Stage III with gross residual disease or stage IV patients	Control group: -Cycles 1-6: Paclitaxel, 175 mg/m <sup>2</sup> Carboplatin, AUC 6 Placebo (starting in cycle 2) (every 3 weeks) -Cycles 7-22: Placebo (every 3 weeks)	10.3	39.3	6.6	7.2	0.7	1.2
		Study group 1: -Cycles 1-6: Paclitaxel, 175 mg/m <sup>2</sup> Carboplatin, AUC 6 Bevacizumab, 15mg/kg (starting in cycle 2) (every 3 weeks) -Cycles 7-22: Placebo (every 3 weeks)	11.2	38.7	6.0	16.5	0.7	2.8
		Study group 2: -Cycles 1-6: Paclitaxel, 175 mg/m <sup>2</sup> Carboplatin, AUC 6 Bevacizumab, 15mg/kg (starting in cycle 2) (every 3 weeks) -Cycles 7-22: Bevacizumab, 15mg/kg (every 3 weeks)	14.1	39.7	7.4	22.9	1.6	2.6
ICON-7 [26] (n=1,528)	Stage I-IIA (grade 3 or clear cell), stage IIB/C-III-IV	Control group: -Cycles 1-5/6: Paclitaxel, 175 mg/m <sup>2</sup> Carboplatin, AUC 5/6 (every 3 weeks)	17.4	44.6	5.6	2.1	0.1	0.4
		Study group: -Cycles 1-5/6: Paclitaxel, 175 mg/m <sup>2</sup> Carboplatin, AUC 5/6 Bevacizumab 7.5 mg/kg (every 3 weeks) -Additional 12 cycles or until disease progression: Bevacizumab 7.5 mg/kg (every 3 weeks)	19.8	44.5	10.3	18.3	0.5	1.3

OCEANS [31] (n=484)	Patients with platinum-sensitive disease (recurrence $\geq$ 6 months after front-line platinum-based therapy) and measurable disease	Control group: -Cycles 1-6/10: Carboplatin, AUC mg/ml/min on day 1 Gemcitabine, 1.000mg/m <sup>2</sup> on day1 and day 8 Placebo on day 1 (untill disease progression) (every 3 weeks)	8.4	33.7*	3.5	0.4	0.9	0.0
		Study group: Cycles 1-6/10: Carboplatin , AUC 4 mg/ml/min on day 1 Gemcitabine, 1.000mg/m <sup>2</sup> on day1 and day 8 Bevacizumab 15 mg/kg on day 1 (until disease progression) (every 3 weeks)	12.4	33.4*	6.8	17.4	8.5	0.0
AURELIA [32] (n=361)	Patients with platinum resistant disease (recurrence within 6 months of completing $\geq$ four cycles of platinum-based therapy)	Control group: Paclitaxel, 80 mg/m <sup>2</sup> on day 1, 8, 15 and 22 (every 4 weeks) or Topotecan 4 mg/m <sup>2</sup> on day 1,8 and 15 (every 4 weeks) or Topotecan 1.25 mg/m <sup>2</sup> on day 1 to 5 ( every 3 weeks) or PLD 40 mg/m <sup>2</sup> on day 1 (every 4 weeks)	3.4	13.3	4.4	6.6	0.6	0.0
		Study group: Paclitaxel, 80 mg/m <sup>2</sup> on day 1, 8, 15 and 22 (every 4 weeks) or Topotecan 4 mg/m <sup>2</sup> on day 1,8 and 15 (every 4 weeks) or Topotecan 1.25 mg/m <sup>2</sup> on day 1 to 5 (every 3 weeks) or PLD 40 mg/m <sup>2</sup> on day 1 (every 4 weeks) + Bevacizumab 10 mg/kg (every 2 weeks) or 15 mg/kg (every 3 weeks) in patients receiving topotecan in the schedule repeated every 3 weeks)	6.7	16.6	5.0	20.1	10.6	2.2

\*interim data: according to preliminary results, PFS: progression-free survival, OS: overall survival, PLD: pegylated liposomal doxorubicin

ovarian or primary peritoneal cancer in complete remission after platinum/taxane based first-line therapy also failed to improve PFS compared with placebo. In addition, it resulted in significantly higher toxicity [38].

Cediranib is a potent oral tyrosine kinase in-

hibitor that blocks VEGF-1,-2,-3 receptors. The Gynecologic Cancer Intergroup (GCIg) conducted a phase 3 randomized trial (ICON-6) in patients with relapsed platinum-sensitive ovarian cancer. Enrolled were 456 patients who received up to 6 cycles of carboplatin (AUC 5/6) plus paclitaxel

(175 mg/m<sup>2</sup>) which were randomized to placebo, cediranib 20 mg/day concurrently with carboplatin plus paclitaxel followed by placebo for up to 18 months or until progression, and cediranib concurrently with carboplatin plus paclitaxel followed by maintenance cediranib. The results were released at the 2013 European Cancer Conference and showed cediranib concurrent with CT improved PFS and when continued with cediranib maintenance, it improved both PFS and OS. Adverse events were significantly more common in the cediranib maintenance arm. ICON-6 was the first trial to demonstrate a significant improvement in the PFS and OS in response to an oral VEGF tyrosine kinase inhibitor. The final results of the study are expected [39].

Polyadenosine 5'phosphoribose polymerase (PARP) plays an essential role in the repair of single-stranded DNA breaks, through the base excision-repair pathway. Olaparib (AZD2281) is a novel oral promising PARP inhibitor which selectively targets homologous recombination repair defective cells such as BRCA deficient tumors with or without BRCA1 or BRCA2 germline mutations [40,41]. A randomized double-blind placebo-controlled phase 2 trial was conducted in 265 patients who received olaparib 400 mg bd as maintenance therapy and who had attained a clinical response or stable disease following a second-line platinum-based CT. The results revealed strikingly improved median PFS (8.4 vs 4.8 months, respectively), especially in the BRCA+ subgroup (11.2 vs 4.3 months) [42,43]. However, the results of OS are immature. At the second interim analysis (58% maturity), OS seemed not to differ between the groups either for patients with mutated BRCA or for those with wild-type BRCA [43]. Adverse events were more commonly reported in the olaparib group than in the placebo group. The most common grade 3 or worse adverse events in the olaparib group were fatigue (7% of the patients in the olaparib group vs 3% in the placebo group) and anaemia (5 vs <1%). Serious adverse events were reported in 18% of the patients who received olaparib and 9% in those who received placebo. Tolerance was similar in patients with mutated BRCA and the overall population. Olaparib also showed no effect on the quality of life during maintenance when compared with placebo. These results led to FDA approval of olaparib in December 2004 as monotherapy for the maintenance treatment of patients with deleterious or suspected deleterious germline mutated BRCA (as detected by an FDA-approved test) advanced ovarian

cancer who have been treated with three or more prior lines of chemotherapy. EMA approved the drug, indicated for use in the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous EOC. In this manner, olaparib was suggested as the first potential personalized treatment option for women with relapsed ovarian cancer with germline BRCA mutation.

In another open-label, phase 2 study patients with platinum-sensitive, recurrent, high-grade serous EOC who had received up to three previous courses of platinum-based CT and who were progression-free for at least 6 months were randomized to either olaparib (200 mg capsules twice daily, orally on days 1–10 of each 21-day cycle) plus paclitaxel and carboplatin for 6 cycles (18 weeks), followed by olaparib monotherapy (400 mg capsules twice daily, given continuously until progression) or paclitaxel and carboplatin for 6 cycles (18 weeks) followed by no further treatment. PFS was significantly longer in the olaparib plus CT group than in the CT alone group (median 12.2 vs 9.6 months), especially in patients with BRCA mutations. Adverse events were mostly grade 1-2 alopecia, nausea, neutropenia, diarrhoea, headache, neuropathy, and dyspepsia and were reported at least 10% more frequently with olaparib plus CT than with CT alone. The most common grade 3 or higher adverse events during the combination phase were neutropenia (43% of the patients in the olaparib plus CT group vs 35% in the CT alone group) and anaemia (9 vs 7%) [44].

SOLO1 and SOLO2 are double-blind multicenter studies in which patients who have a known deleterious BRCA mutation and who are in complete or partial response following the completion of platinum-based CT are being randomized to receive olaparib (300 mg bid) or placebo. These studies have been recently initiated. SOLO-1, as distinct from PARP inhibitors, tests the administration of olaparib vs placebo as maintenance therapy after frontline therapy in patients with BRCA 1 or 2 germline mutation, not in the context of relapsed disease. To be included in SOLO1, patients must have newly diagnosed advanced disease and have responded to first-line platinum therapy, whereas patients in SOLO2 must have completed  $\geq 2$  lines of platinum therapy [45]. The results of these studies are eagerly awaited.

The randomized clinical trials investigating some of the new agents for maintenance therapy of ovarian cancer are summarized in Table 2.

**Table 2.** New agents under investigation for maintenance therapy of ovarian cancer

Trial	Agent	Patient population	Treatment arms	Median PFS (months)	Median OS (months)
AGO-OVAR 16 [35] (n=940)	Pazopanib	Stage II-IV EOC, no evidence of progression after primary therapy consisting of surgery and at least five cycles of platinum-taxane chemotherapy	Study group: Following primary systemic platinum-based chemotherapy therapy; followed by Pazopanib 800 mg once per day for up to 12-24 months as maintenance	17.9	*An interim analysis of OS showed no significant difference between groups
			Control group: Following primary systemic platinum-based chemotherapy therapy, followed by placebo	12.3	
AGO-OVAR 12/ LUME-OVAR-1 [37] (n=1,366)	Nintedanib	Stage IIB-IV EOC after initial debulking surgery, or with only biopsy for patients with stage IV in whom surgery was not considered as an option.	Study group: Paclitaxel (175 mg/m <sup>2</sup> )/ carboplatin (AUC 5 or 6) with nintedanib (200 mg twice per day) every 3 weeks for six cycles followed by maintenance therapy with nintedanib for 120 weeks (including the period of concurrence with chemotherapy)	17.3	*An interim analysis of OS (20% maturity) showed no significant difference between groups
			Control group: Paclitaxel (175 mg/m <sup>2</sup> )/ carboplatin (AUC 5 or 6) with placebo every 3 weeks for six cycles followed by maintenance therapy with placebo	16.6	
ICON-6 [41] (n=456)	Cediranib	Recurrent platinum-sensitive EOC patients at first relapse	Study group 1: Platinum-based chemotherapy for 6 cycles plus cediranib (20mg/day), followed by placebo maintenance therapy for up to 18 months or until progression	11.4	*An interim analysis of OS showed median OS was 17.6 vs 20.3 platinum-based chemotherapy and cediranib throughout arms respectively.
			Study group 2: Platinum-based chemotherapy for 6 cycles plus cediranib (20 mg /day), followed by cediranib maintenance therapy for up to 18 months or until progression	12.6	
			Control group: Platinum-based chemotherapy for 6 cycles plus placebo, followed by placebo maintenance therapy	9.4	
Ledermann et al. [44] (n=265)	Olaparib	Recurrent platinum-sensitive EOC patients who had received two or more platinum-based regimens and had had a partial or complete response to their most recent platinum-based regimen.	Study group: Olaparib 400mg twice a daily within 8 weeks after completion of last dose of platinum-based chemotherapy	8.4	*An interim analysis of OS (38% maturity) showed no significant difference between groups
			Control group: Placebo within 8 weeks after completion of last dose of platinum-based chemotherapy	4.8	

\*interim data according to preliminary results; PFS: progression-free survival, OS: overall survival, EOC: epithelial ovarian cancer



## Conclusion

The efficacy of maintenance treatment is still unclear and includes concerns for both short-term and longer-term side effects. The investigators are in search for alternative agents, dosages, treatment intervals and periods to improve both survival outcomes and QoL. In this process, introduction of targeted agents has changed the direction of researches and more details about carcinogenesis have been clarified. The most promising agents for maintenance treatment seem the angiogenesis inhibitors and PARP inhibitors; however, there is not adequate evidence of their favorable effects on OS yet. On the other hand, PFS is regarded as a more valuable endpoint to decide whether a treatment option is effective or not and most trials use PFS instead of OS as primary endpoint. This is because, especially in recurrent ovarian cancer,

improvements of OS do not depend only on the investigated drug but also on subsequent treatment lines and cross-over effects. This is a serious reason why bevacizumab and olaparib are getting place in important Cancer Societies' guidelines as maintenance agents under some certain conditions. However, maintenance therapy is still not recommended as a standard of care in ovarian cancer and there is a lack of consensus between the guidelines. Further results from ongoing studies for PFS, OS and QoL are eagerly awaited.

## Authors' contribution

Kilic Sakarya D: Project development, data collection, data reviewing, manuscript writing/editing.

Yetimalar MH: Project development, manuscript writing/editing.

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