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Review

Randomized Clinical Trials and Real World Prospective Observational Studies on Bevacizumab, PARP Inhibitors, and Immune Checkpoint Inhibitors in the First-Line Treatment of Advanced Ovarian Carcinoma: A Critical Review

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Abstract. *Platinum/paclitaxel-based chemotherapy is able to obtain a clinical response in up to 80% of patients with advanced ovarian carcinoma, but most of them will subsequently develop recurrent disease. Several therapeutic approaches, including prolonged administration of the first-line regimen and the concomitant or sequential addition of a third cytotoxic agent to standard chemotherapy, failed to improve the clinical outcome of patients. In the last years, the implementation of the biological knowledge on ovarian carcinoma and the introduction of bevacizumab (BEV) and poly(ADP-ribose) polymerase inhibitors (PARPi) in first-line treatment have improved patient prognosis. In this review, we have analyzed the randomized clinical trials and real world observational studies on these issues, with the aim to suggest an algorithm for a rational use of BEV and PARPi in patients with newly diagnosed advanced ovarian carcinoma.*

GLOBOCAN estimates of the worldwide incidence and mortality of 36 cancers in 185 countries have shown 295,414 new cases of ovarian carcinoma and 184,799 deaths due to this malignancy in 2018 (1). After Kurman and Shih's proposal of a dualistic model for ovarian carcinogenesis, several molecular and histopathologic studies have provided novel important insights into the molecular pathogenesis of this disease (2). Nowadays ovarian carcinomas can be subdivided into five histological subtypes, termed high-grade serous (70%), endometrioid (10%), clear cell (10%), mucinous (3%), and low-grade serous (<5%) carcinomas (3). The large majority of these malignancies are high-grade tumors, with aggressive clinical behavior and advanced stage at presentation.

Primary debulking surgery (PDS) followed by paclitaxel (PTX)/carboplatin (CBDCA)-based chemotherapy is the best treatment modality for advanced ovarian carcinoma, if the resection of all macroscopic disease can be obtained with an acceptable operative morbidity (4). Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and additional chemotherapy is usually suggested for patients not fit for primary aggressive surgery due to either advanced age, frailty, poor performance status and comorbidities or disease spread that is unlikely to be optimally debulked (5, 6). Histopathologic diagnosis of ovarian carcinoma based on surgical or diagnostic imaging-technique guided tissue biopsies is recommended before starting NACT. Whenever biopsy is not feasible, the diagnosis should be based on the cytological examination of peritoneal or pleural effusion combined with a serum CA125/CEA ratio >25, and possibly on gastroscopy and colonoscopy negative for primary gastro-enteric tumors (7).

Standard chemotherapy is able to achieve a clinical response rate of 59-81.4% with a median progression-free survival (PFS) of 15.5-22 months and a median overall survival (OS) of 31-44 months (8-13). Approximately 75% of the responding patients will develop recurrent /progressive disease within a median time of 18-24 months, and different consolidation or maintenance treatments, such as whole abdomen radiotherapy, intraperitoneal chemotherapy, high-dose chemotherapy with hematopoietic support, prolonged administration of the first-line regimen and the concomitant or sequential addition of a

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third cytotoxic agent to standard PTX/CBDCA, failed to improve the clinical outcomes (14-19).

In recent years the implementation of biological knowledge on ovarian carcinoma and especially on the predictive and prognostic relevance of *BRCA* and homologous recombination status, as well as the addition of biological agents, such as BEV and poly(ADP-ribose) polymerase inhibitors (PARPi) to first-line chemotherapy have improved patient prognosis.

In this review we analyze the clinical trials on these issues, in order to offer a possible algorithm that may help the clinicians in the rational use of BEV and PARPi in patients with newly diagnosed advanced ovarian carcinoma.

Trials With Bevacizumab

Gynecologic Oncology Group (GOG) 218 phase III trial randomized patients with advanced ovarian carcinoma to receive i) PTX+CBDCA for 6 cycles with placebo added in cycles 2 through 22; or ii) the same chemotherapy plus BEV added in cycles 2 through 6 and followed by placebo added in cycles 7 through 22; or iii) the same chemotherapy plus BEV added in cycles 2 through 22 (20) (BEV throughout). The BEV-throughout arm achieved a better PFS compared with the chemotherapy arm alone [hazard ratio (HR)=0.717, $p<0.001$], which was the primary endpoint of the study (Table I and Table II).

Grade ≥2 hypertension was significantly more common with BEV than with placebo, whereas there were no significant differences among the three arms in terms of severe gastrointestinal adverse events or proteinuria. The final analysis of the study confirmed the lack of OS benefit from both concurrent BEV and concurrent and maintenance BEV compared with chemotherapy only in the whole population (HR=1.06, 95%CI=0.94-1.20 and HR=0.96, 95%CI=0.85-1.09, respectively) (21). However, in an exploratory subset analysis the BEV-throughout arm was associated with a better OS compared with the chemotherapy only arm in patients with stage IV disease (median, 42.8 *versus* 32.6 months, HR=0.75; 95%CI=0.59-0.95).

In the International Collaboration on Ovarian Neoplasms (ICON7) trial, patients with high-risk stage IA-IIA or stage IIB-IV ovarian carcinoma were randomized to PTX+CBDCA for 6 cycles or the same chemotherapy plus BEV 7.5 mg/kg given concurrently for 5 or 6 cycles and continued for 12 additional cycles (22) (Table I). PFS was better for the BEV arm (HR=0.81, $p=0.004$), and the PFS difference between BEV- and non-BEV-treated patients peaked at 12 months, corresponding to the end of BEV treatment, with an improvement in PFS at this time of approximately 15.1% but afterwards this advantage tended to decrease (Table II). In a subsequent exploratory analysis, the addition of BEV improved OS (median, 39.7 *versus* 30.2 months, $p=0.03$) in a subgroup of 502 high-risk patients, defined as those with stage IV disease, or suboptimally debulked (>1 cm) stage III disease, or inoperable disease (23). In a further update of the trial, the PFS benefit from the antiangiogenic agent was 0.77 (95%CI=0.59-0.99) for the patients with stage IIIB-IV and no macroscopic RD and 0.81 (95%CI=0.69-0.95) for those with stage IIIB-IV disease and macroscopic RD (24).

Real world data were consistent with the results of these two randomized trials (25-29) (Table III).

The OTILIA prospective observational study has been planned to assess the safety, efficacy, quality of life and predictive/selection factors for BEV in combination with PTX+CBDCA in first-line treatment of 1090 patients with advanced ovarian carcinoma. Patient recruitment was completed in September 2019 but no study results have been yet posted on ClinicalTrials.gov (25).

The OSCAR study assessed 229 British women with high-risk stage IIIB-IV ovarian carcinoma who received BEV [7.5 or 15 mg/kg every 3 weeks (Q3W)] concurrently with first-line chemotherapy and sequentially as maintenance therapy (26). In the whole population the median PFS was 15.4 months similar to that of the high-risk subgroup of the ICON7 trial. Median PFS was 20.8, 16.1 and 13.6 months, respectively, in patients who underwent PDS, IDS and no surgery, and the most frequent grade 3-4 adverse event was hypertension (16%).

The JGOG3022 prospective Japanese study by Komiyama *et al*. (27) assessed 293 patients with stage III-IV ovarian carcinoma who received PTX+CBDCA + concurrent and maintenance BEV with the same schedule and dosages as the GOG 218 trial. Median PFS was 16.3 months and response rate among the patients with measurable disease was 77.5%, ranging from 81.7% in patients with serous histology to 63.6% in those with clear cell histology. A phase III trial of first-line chemotherapy in ovarian clear cell carcinoma reported a response rate of 46.7% to PTX+CBDCA (30). Therefore, the addition of BEV appeared to increase the anticancer activity of standard chemotherapy in this chemoresistant histotype. In the study of Komiyama *et al*. (27) grade >3 hypertension, proteinuria, gastrointestinal events and thromboembolic events were reported in 23.2%, 12.6%, 1% and 1.4% of the cases, respectively.

The real world ROBOT trial reviewed 381 consecutive patients with ovarian carcinoma who received first-line PTX/CBDCA-based chemotherapy without BEV (n=304) or with BEV (n=77) at doses ranging from 7.5 to 15.1 mg/kg (28). One hundred and forty-seven (38.6%) patients were in stage I-II, 234 (61.4%) were in stage III-IV, and of these 116 were at high-risk according to ICON7 criteria. The addition of BEV to chemotherapy showed a trend towards a better PFS in the whole group of patients with advanced disease (median, 11.6 *versus* 9.3 months, HR=0.84, 95%CI=0.6-

Table I. *Incorporation of BEV in first-line therapy of ovarian carcinoma: Randomized trials. Tumor stage and randomization arms.*

Trial	Pts	Stage	Regimen	arm
GOG 218	1873	III (macroscopic RD)	CBDCA + PTX[a] + PL[b]→PL maintenance[b]	Control
		IV	CBDCA+PTX[a] +BEV[c] → PL maintenance[c]	BEV-initiation
			CBDCA+PTX[a]+BEV[d] →BEV maintenance[d]	BEV-throughout
ICON7	1528	I-IIa (G3, clear cell)	CBDCA+PTX[e]	
		IIb-IV	CBDCA+PTX[e]+BEV[f] → BEV maintenance[f]	

[a]CBDCA AUC 6 +PTX 175 mg/m^2 Q3w × 6 cycles; [b]PL Q3w added in cycles 2 through 22; [c]BEV (15 mg/kg Q3w) added in cycles 2 through 6 and PL added in cycles 7 through 22; [d]BEV (15 mg/kg Q3w) added in cycles 2 through 22; [e]CBDCA AUC 5-6 + PTX 175 mg/m2 Q3w × 6 cycles; [f]BEV (7.5 mg/kg Q3w) given concurrently for 5-6 cycles and continued for 12 additional cycles. CBDCA: Carboplatin; PTX: paclitaxel; PL: placebo; BEV: bevacizumab; Q3W: every 3 weeks; AUC: area under curve; RD: residual disease.

Table II. *Incorporation of BEV in first-line therapy of ovarian carcinoma: Randomized trials. Clinical outcome and BEV-related severe adverse events.*

Trial	Arm	PFS median	OS median	GI[ç] ≥2	HT ≥2	Proteinuria ≥3	VT	AT	Bleeding		Wound disruption
									CNS	No CNS	
GOG 218	Control	10.3	39.3	1.2%	7.2%	0.7%	5.8%	0.8%	0%	0.8%	2.8%
	BEV-initiation	11.2°	38.7°°	2.8%	16.5%	0.7%	5.3%	0.7%	0%	1.3%	3.6%
	BEV-throughout	14.1*	39.7**	2.6%	22.9%^	1.6%	6.7%	0.7%	0.3%	2.1%	3.0%
ICON7	Control	20.3	NR	<1%	<1%	<1%	4%	<2%	0%	<6%	<3%
	BEV-throughout	21.8[§]	NR[§§]	1%	6%	1%	6%	4%	1%	<8%	5%

Primary endpoint: *versus* control: HR=0.908 (95%CI=0.795-1.040)°, HR=1.036 (95%CI=0.827-1.297)°°; *versus* control: HR=0.717 (95%CI=0.625-0.824)*, HR=0.915 (95%CI=0.727-1.152; p=0.45)**; *versus* control: p<0.05^; *versus* control: HR=0.81; 95%CI=0.70-0.94)§; HR=0.85 (95%CI=0.69-1.04)[§§]. [ç]Gastro-intestinal adverse events: perforation, fistula, necrosis of anastomotic leak. PFS: progression fee survival; OS: overall survival; GI: gastrointestinal; HT: hypertension; VT: venous thrombosis; AT: arterial thrombosis; CNS: central nervous system.

1.19) and significantly improved PFS in high-risk patients (median, 10.5 *versus* 6.0 months, HR=0.62, 95%CI=0.39-0.97). Moreover, there was a trend towards a better OS for BEV-treated patients both in the whole advanced stage subgroup (median, not reached *versus* 43.7 months, HR=0.69, 95%CI=0.43-1.11) and in the high-risk subset (median, not reached *versus* 34.7 months, HR=0.61, 95%CI=0.33-1.10). Low rates and grades of BEV-related adverse events were recorded.

ROSiA is a prospective single-arm phase 3b study which assessed the efficacy and safety of BEV-containing treatment in 1021 patients with grade 3 stage I-IIA or stage IIB-IV ovarian carcinoma without signs or symptoms of gastrointestinal obstruction or history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the preceding 6 months (29). Eligibility criteria were designed to recruit a patient population similar to that enrolled in the ICON7 trial. After surgery, patients received BEV (15 mg/kg) (89%) or 7.5 mg/kg (11%) Q3W concurrently with PTX (175 mg/m^2 Q3W or 80 mg/m^2 weekly) + CBDCA (AUC 5-6 Q3W) for 4-8 cycles, followed by BEV maintenance for up to 24 months. This antiangiogenic agent was administered for more than 1 year in 62% of the patients, more than 15 months in 53%, and more than 2 years in 29%. Median PFS was 25.5 months, the longest reported in the literature, in the whole series, 18.3 months in high-risk patients and 32.0 months in non-high-risk patients according to ICON7 criteria. Grade ≥3 hypertension, proteinuria and gastrointestinal events occurred in 25%, 4% and 1.4% of the patients, respectively. Typically, hypertension first appeared during earlier BEV cycles, with a median time to onset of 2.1 months, whereas proteinuria showed a more linear relationship between first onset and duration of exposure for the first 24 months. Therefore, extended BEV-containing therapy appeared to be both tolerable and feasible.

The MITO 16A- MaNGO OV2A phase 4 trial included 398 patients with advanced ovarian carcinoma who received CBDCA (AUC 5) + PTX (175 mg/m^2) + BEV (15 mg/kg) Q3W for 6 cycles followed by BEV maintenance until 22 cycles (31). After a median follow-up of 32.3 months, median PFS was 20.8 months and median OS was 41.1 months and toxicity profile wase comparable to previous

Table III. *Incorporation of BEV in first- line therapy of ovarian carcinoma: Real World observational studies.*

NCT01697488:	Non-interventional surveillance study on first-line bevacizumab in combination with carboplatin/paclitaxel in patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (OTILIA)
NCT01863693:	Observational study of bevacizumab in combination with chemotherapy as first-line treatment in patients with advanced ovarian cancer (OSCAR 1)
JGOG3022:	Bevacizumab combined with platinum–taxane chemotherapy as first-line treatment for advanced ovarian cancer: a prospective observational study of safety and efficacy in Japanese patients
ROBOT TRIAL:	Real-world study of adding bevacizumab to chemotherapy for ovarian, tubal, and peritoneal cancer as front-line or relapse therapy
NCT01239732:	Global study to assess the addition of bevacizumab to carboplatin and paclitaxel as front-line treatment of epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma (ROSiA)
NCT01706120:	Study of clinical and biological prognostic factors in patients with ovarian cancer receiving carboplatin+paclitaxel with bevacizumab (MITO16/MANGO-2)
NCT0146289:	A prospective randomised phase III trial to evaluate optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer (BOOST)

data. Neither baseline blood pressure nor the development of hypertension during BEV had prognostic relevance.

The NCT01462890 prospective phase III trial randomly allocated 927 women with stage IIB-IV ovarian carcinoma treated with PDS followed by PTX (175 mg/m^2) + CBDCA (AUC 5) + BEV (15 mg/kg) Q3W to receive BEV for either 15 months or 30 months (32). There was no difference between the two arms in terms of both PFS (median, 24.2 *versus* 26.0 months; HR=0.99, 95%CI=0.85-1.15) and OS (median, 54.3 *versus* 60.0 months; HR=1.04; 95%CI=0.87-1.23).

The non-comparative phase II ANTHALYA trial randomized 95 patients in a ratio 2:1 to receive either NACT with CBDCA (AUC 5) + PTX (175 mg/m^2) Q3W for 4 cycles or the same NACT plus BEV (15 mg/kg) Q3W on cycles 1-3 prior to IDS (33). The BEV–arm achieved a complete response rate of 58.6% with a lower confidence limit of 47.0%, which was higher than the threshold of 45% established on the basis of the complete response rate in the Vergote *et al.*'s randomized trial of NACT followed by IDS (46.3%) (34). The incidence of post-surgical adverse events, mainly represented by wound, infectious, and gastrointestinal complications, was similar in the two arms. Therefore, the addition of BEV to NACT appeared to be safe, although the evidence that it improves the clinical outcome of patients is still lacking.

Trials With PARP Inhibitors

Four phase III randomized trials have demonstrated the efficacy and acceptable toxicity profile of the introduction of PARPi in the first-line treatment of advanced ovarian carcinoma (Table IV and Table V).

SOLO-1 trial randomly assigned patients with germline or somatic *BRCA* mutation in complete or partial response after first-line platinum-based chemotherapy to receive either olaparib or placebo as maintenance (35). In the primary investigator analysis 3-years PFS was 60% and 27% for the olaparib arm and placebo arm, respectively (HR=0.30; p<0.001). The blinded independent central review confirmed these results: 3-year PFS was 69% for olaparib compared with 35% for placebo (HR=0.28; 95%CI=0.20-0.39, p<0.001). At an interim analysis 3-year OS was similar in the two groups (84% *versus* 80%; HR=0.95; 95%CI=0.60-1.53). G3-4 anemia was the most common adverse event in the olaparib group (22%). Myeloid acute leukemia, novel primary cancer, and pneumonitis or interstitial lung disease occurred in 1%, 2%, and 2% of patients, respectively, in the olaparib arm, compared to 0%, 2%, and 0% of those, respectively, in the placebo arm. All three cases of acute myeloid leukemia were diagnosed more than 30 days after olaparib treatment completion. On December 2018, the U.S. Food and Drug Administration (FDA) granted approval to olaparib monotherapy for first-line maintenance of *BRCA*-mutated advanced ovarian carcinoma. An update of the study confirmed that olaparib significantly improved PFS (median, 56 *versus* 13.8 months; 5-year PFS, 48% *versus* 21%, HR=0.33, 95%CI=0.25-0.43) (36). A subgroup analysis found that olaparib maintenance reduced the risk of progression or death in patients who underwent PDS (HR=0.31; 95%CI=0.21-0.46) and in those who underwent IDS (HR=0.37; 95%CI=0.24-0.58), in patients with RD after surgery (HR=0.44; 95%CI=0.25-0.77) and in those without RD after surgery (HR=0.33; 95%CI=0.23-0.46), in complete responders (HR=0.34, 95%CI=0.24-0.47) and in partial responders at baseline (HR=0.31; 95%CI=0.18-0.52), and in patients with *BRCA1* mutation (HR=0.41; 95%CI=0.30-0.56) as well as in those with *BRCA2* mutations (HR=0.20; 95%CI=0.10-0.37) (37). These PFS improvements were obtained without clinically meaningful changes in health-related quality of life (38).

PRIMA trial randomized patients in clinical response after 6 to 9 cycles of first-line platinum-based chemotherapy to

Table IV. *PARP inhibitors in first-line therapy of ovarian carcinoma: Randomized trials. Patient characteristics and randomization arms.*

Trial	Arm	Randomization	pts	Stage IV	BRCA	PDS	No RD	Clinical CR after CT
SOLO-1	Olaparib[a] 300 mg bid PL[a]	2:1	391	17%	100%	63%	22%	82%
PAOLA1	Olaparib 300 mg bid up to 24 months + BEV 15 mg/kg q3w up to 15 months PL bid up to 24 months + BEV 15 mg/kg q3w up to 15 months	2:1	1806	30%	29%	51%	35%	73%
PRIMA	Niraparib 300 mgb daily up to 36 months PL daily up to 36 months	2:1	733	35%	30%	33%	NA	69%
VELIA	CBDCA + PTXc + PLd →PLe (Control) CBDCA + PTXc + VELf →PLe (VEL-initiation) CBDCA + PTXc + VELf →VELg (VEL-throughout)	1:1:1	1140	23%	26%	67% PDS	47%	NA

[a]Pts NED at 2 years stopped, partial responders allowed to continue trial intervention in a blinder manner; [b]After November 2017 individualized starting dose of 200 mg for pts with baseline body weight <77 kg or platelet count <150,000 mm^3; [c]175 mg/m^2 q3w or 80 mg/m^2 weekly + CBDCA AUC 6 q3w; [d]PL concomitant with chemotherapy; [e]PL as maintenance; [f]VEL (150 mg bid) concomitant with chemotherapy; [g]VEL (300-400 mg bid) as maintenance. Pts: Patients; PDS: primary debulking surgery; RD: residual disease; CR: complete response; CT: chemotherapy, PL: placebo; bid: twice daily, BEV: bevacizumab; Q3W: every 3 weeks; NA: not available; IDS; interval surgery; CBDCA: carboplatin; PTX: paclitaxel; VEL: veliparib; AUC: area under curve.

receive to either niraparib or placebo as maintenance (39). Most patients had stage III disease with visible RD after PDS, inoperable stage III disease or stage IV disease, and had undergone NACT followed by IDS. Tumor samples underwent central testing to identify those with homologous-recombination deficiency (HRD), according to myChoice assay based on three genomic lesions, *i.e.,* loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions. HRD was defined as the presence of *BRCA* mutation, myChoice assay score ≥42 or both. A hierarchical-testing method was performed for the primary end point in patients with HRD, followed by a test in the overall population. Niraparib improved PFS both in patients with HRD (HR=0.43, $p<0.001$) and in overall population (HR=0.62; $p<0.001$). Moreover, prespecified exploratory analyses revealed that niraparib maintenance was associated with a significantly longer PFS in patients with HRD and *BRCA* mutation (HR=0.40), in those with HRD but without *BRCA* mutation (HR=0.50) and in those with homologous-recombination proficiency (HRP) (HR=0.68). Moreover, niraparib improved PFS also in other subsets of patients with poor prognosis, such as those who underwent NACT (median, 13.9 *versus* 8.2 months; HR=0.59; 95%CI=0.46-0.76) and those with a partial response to chemotherapy (median, 8.3 *versus* 5.6 months; HR=0.60; 95%CI=0.43-0.85). The interim analysis of 24 month-OS data failed to detect a benefit from niraparib both in the overall population (84% *versus* 77%; HR=0.70; 95%CI=0.44-1.11) and in HRD patients (91% *versus* 85%, HR=0.61; 95%CI=0.27-1.39). G3-4 anemia and thrombocytopenia were the most common adverse events in niraparib arm, and myelodysplastic syndrome occurred in a patient treated with this PARPi. The populations of SOLO-1 and PRIMA trials were quite different, not only as for *BRCA* or HRD status. More patients in SOLO-1 than in PRIMA had stage III disease (83% *versus* 65%) and underwent PDS with no macroscopic RD (44% *versus* 0.4%). However, subgroup analysis showed a similar lower risk of progression (36) in olaparib-treated patients with RD after surgery in the SOLO-1 trial and in niraparib-treated patients with *BRCA* mutation and RD after surgery in the PRIMA trial (HR=0.44, 95%CI=0.25-0.77, and, respectively, HR=0.40, 95%CI=0.27-0.62).

A post-hoc analysis of the PRIMA trial presented by O'Cearbhaill at the Society of Gynecologic Oncology (SGO) meeting 2021 showed that niraparib treatment reduced the risk of progression compared with placebo in the whole population of patients who underwent PDS (median PFS, 13.7 *versus* 8.2 months, HR=0.67, 95%CI=0.468-0.964) and in the patients who underwent PDS with visible RD (median PFS, 11.8 *versus* 7.8 months, HR=0.58, 95%CI=0.391-0.864). Moreover, niraparib maintenance significantly improved PFS in the whole population of patients who underwent IDS (median, 14.2 *versus* 8.2 months, HR=0.57, 95%CI=0.441-0.731), in the patients who underwent IDS with visible RD (median, 11.1 *versus* 5.6 months, HR=0.41, 95%CI=0.269-0.620) and in those who underwent IDS with no visible RD (median, 18.2 *versus* 10.9 months, HR=0.65, 95%CI=0.461-0.91).

PAOLA-1 trial randomly assigned patients in response after first-line treatment with platinum-taxane + BEV to

Table V. *PARP inhibitors in first-line therapy of ovarian carcinoma: Randomized trials. Clinical outcome and PARP-I related grade 3-adverse events.*

Trial	Arm	PFS median	HR 95% CI	Anemia	Neutropenia	Thrombocytopenia	Fatigue	Vomiting
SOLO-1	Olaparib	Not reached	0.30 (0.23-0.41)	22%	9%	1%	4%	<1%
	PL	13.8		2%	5%	2%	2%	<1%
PAOLA1	Olaparib + BEV	22.1[a]	0.59 (0.49-0.72)	17%	6%	2%	5%	1%
	PL + BEV	16.6		1%	3%	<1%	1%	2%
	Olaparib + BEV	37.2[b]	0.33 (0.25-0.45)					
	PL + BEV	17.7						
	Olaparib + BEV	28.1[c]	0.43 (0.28-0.66)					
	PL + BEV	16.6						
	Olaparib + BEV	16.6[d]	1.00 (0.75-1.35)					
	PL + BEV	16.2						
PRIMA	Niraparib	21.9[e]	0.43 (0.31-0.59)	31%	12.8%	28.7%	1.9%	0.8%
	PL	10.4		1.6%	1.2%	0.4%	0.4%	0.8%
	Niraparib	13.8[f]	0.62 (0.50-0.76)					
	PL	8.2						
	Niraparib	22.1[g]	0.40 (0.27-0.62)					
	PL	10.9						
	Niraparib	19.6[h]	0.50 (0.31-0.83)					
	PL	8.2						
	Niraparib	8.1[i]	0.68 (0.49-0.94)					
	PL	5.4						
VELIA	Vel-throughout	34.7[l]	0.44 (0.28-0.68)	38%	58%	28%	8%	4%
	VEL-combi	21.1	1.22 (0.82-1.80)	41%	62%	31%	5%	4%
	Control	22.0		26%	49%	8%	3%	2%
	Vel-throughout	31.9[m]	0.57 (0.43-0.76)					
	VEL-combi	18.1	1.10 (0.86-1.41)					
	Control	20.5						
	Vel-throughout	23.5[n]	0.68 (0.56-0.83)					
	VEL-combi	15.2	1.07 (0.90-1.29)					
	Control	17.3						
	Vel-throughout	15.0[o]	0.81 (0.60-1.09)					
	VEL-combi	12.9						
	Control	11.5	1.04 (0.78-1.39)					

[a]Intention to treat population; [b]HRD tumors including those with *BRCA* mutation (Preplanned subgroup analysis); [c]HRD tumors without *BRCA* mutations (Preplanned subgroup analysis); [d]HRP tumors (Preplanned subgroup analysis); [e]HRD tumors; [f]intention to treat population; [g]HRD tumors including those with *BRCA* mutation (Preplanned subgroup analysis); [h]HRD tumors but without *BRCA* mutations (Preplanned subgroup analysis); [i]HRP tumors (Preplanned subgroup analysis); [l]*BRCA* mutation; [m]HRD; [n]intention to treat population; [o]HRP. PFS: Progression-free survival; HR: hazard ratio; 95%CI: 95% confidence interval; PL: placebo; BEV: bevacizumab: HRD: homologous recombination deficiency; HRP: homologous recombinant.

receive either olaparib + BEV or placebo + BEV (40). PDS, IDS and no surgery were performed in 50%, 42% and 7% of the patients in the olaparib + BEV arm and in 51%, 41% and 8% of those in the placebo + BEV arm. Tumor HRD status was determined by myChoice assay. The analysis of intention to treat population revealed a longer PFS in the olaparib + BEV arm (HR=0.59). Moreover, preplanned subgroup analysis found that combined maintenance treatment improved PFS both in patients with HRD tumors including those with *BRCA* mutations (HR=0.33) and in those with HRD tumors that did not have *BRCA* mutations (HR=0.43) but not in patients with HRP tumors. Hypoxia induced by antiangiogenic treatment could induce down-regulation of *BRCA1* and RAD51 and decrease homologous recombination in cancer cells (41-43), and therefore BEV might enhance the activity of olaparib in patients with HRD tumors, and especially in those without *BRCA* mutations (40). An update of the study showed that olaparib + BEV also significantly improved second progression free survival (PFS2) in the intention to treat population (median, 36.5 *versus* 32.6 months, HR=0.78; 95%CI=0.64-0.95), in patients with *BRCA* mutations (median, not reached *versus* 45 months, HR=0.53), in those with HRD tumors (median, 50.3 *versus* 35 months, HR=0.56) and in those with HRD tumors who did not have *BRCA* mutations (median, 50.3 *versus* 30.1 months; HR=0.60), without no new safety signals (44).

At the ASCO meeting 2021, Pautier *et al.* (45) reported that olaparib + BEV improved PFS regardless of stage in

Table VI. *PARP inhibitors in first-line therapy of ovarian carcinoma: Ongoing trials.*

NCT04227522:	Rucaparib maintenance after bevacizumab maintenance following CBDCA-Based first-line chemotherapy in EOC (MAMOC)
NCT04532645:	A pan-European non-interventional, retrospective observational cohort study of pts with *BRCA* mutated FIGO stage III-IV ovarian cancer treated with olaparib tablets in the first-line maintenance
NCT03462212A:	Randomized, molecular driven phase II trial of CBDCA+PTX+BEV *vs*. CBDCA + PTX + BEV + rucaparib *vs*. CBDCA + PTX + rucaparib, selected according to HRD status, in pts with advanced (Stage III B-C-IV) ovarian, primary peritoneal and fallopian tube cancer (MITO 25)

Table VII. *Incorporation of immunotherapy in first-line therapy of ovarian carcinoma: randomized trials*

NCT02718417:	Randomized, open-label, multicenter, phase 3 study to evaluate efficacy and safety of avelumab in combination with and/or following chemotherapy in pts with previously untreated EOC (JAVELIN OVARIAN 100)
NCT03038100:	A phase III, multicenter, randomized, study of atezolizumab *vs*. placebo administered in combination with PTX+ CBDCA + BEV in pts with newly-diagnosed stage III-IV EOC (IMagyn050)
NCT03740165:	A randomized phase 3, double-blind study of chemotherapy with or without pembrolizumab followed by maintenance with olaparib or placebo for the first-line treatment of *BRCA* non-mutated advanced epithelial ovarian cancer (EOC) (KEYLYNK-001/ENGOT-ov43 / GOG-3036)
NCT03522246:	A multicenter, randomized, double-blind, placebo- controlled phase 3 study in ovarian cancer patients evaluating rucaparib and nivolumab as maintenance treatment following response to front-line platinum-based chemotherapy (ATHENA)

patients with HRD tumors (stage III: median, 39.3 *versus* 19.9 months, HR=0.32, 95%CI=0.22-0.47; stage IV: median, 25.1 *versus* 12.8 months, HR=0.32, 95%CI=0.20-0.52). Similarly, the addition of olaparib to BEV maintenance resulted in PFS2 benefit irrespective of stage in the same subgroup of patients (stage III, median: not reached *versus* 43.0 months, HR=0.57, 95%CI=0.38-0.87; stage IV: median, 37.8 *versus* 25.6 months, HR=0.56; 95%CI=0.35-0.91).

G3-4 anemia and fatigue were more common in the olaparib + BEV arm, whereas grade 3 hypertension was more frequent in the placebo + BEV arm (30% *versus* 19%). The incidence of myelodysplastic syndrome, acute myeloid leukemia, or aplastic anemia was 1% in the olaparib group and <1% in the placebo group. The safety profile of olaparib in this trial was consistent with that reported for olaparib in the SOLO-1 trial. On May 2020, FDA approved the combination of olaparib + BEV for first-line maintenance of HRD-positive advanced ovarian carcinoma.

It is difficult to compare the outcome of the patients enrolled in the SOLO-1 trial and of the patients with *BRCA* mutations enrolled in PAOLA-1 trial because of the different baseline characteristics and the lack of a common comparator arm. Vergote *et al*. (46) performed a population adjusted indirect comparison of these trials using a propensity score weighting technique to minimize the differences in the characteristics of the two populations. Two year-PFS rates were 50% and 36%, respectively, (HR=0.65, 95%CI=0.43-0.95) for the PAOLA-1 *BRCA*-mutated patients treated with BEV + placebo and the SOLO-1 patients who received placebo, and 73% and 50% (HR=0.48, 95%CI=0.30-0.75), respectively, for the SOLO-1 patients treated with olaparib and the PAOLA-1 *BRCA*- mutated patients treated with BEV + placebo. On the other hand, the 2-year PFS was not significantly different between the PAOLA-1 *BRCA*-mutated patients treated with BEV + olaparib and SOLO-1 patients treated with olaparib (82% *versus* 73%, HR=0.71, 95%CI=0.45-1.09)

The VELIA trial randomized advanced ovarian carcinoma patients to receive PTX + CBDCA plus concomitant and maintenance placebo (control arm), the same chemotherapy plus concomitant veliparib followed by placebo maintenance (veliparib-combination-only), or the same chemotherapy + concomitant veliparib followed by veliparib maintenance (veliparib throughout) (47). The HRD cohort was defined as the patients who had *BRCA* mutations or HRD tumor at myChoice assay (with a score of ≥33 considered to indicate HRD). According to investigator assessment, the veliparib-throughout arm experienced a longer PFS compared with control arm in the *BRCA*-mutated cohort (HR=0.44, $p<0.001$), in the HRD cohort (HR=0.57, $p<0.001$) and in the intention to treat population (HR=0.68, $p<0.001$), but not in the HRP cohort. The most common adverse event during treatment in

the veliparib-throughout arm was nausea (80%), with most events (90%) being of grade 1 or 2. The incidence of grade 3-4 hematologic toxicity and fatigue are reported in the Table V. One myelodysplastic syndrome developed in the veliparib-combination-only arm, and one acute myeloid leukemia occurred in the veliparib-throughout arm. A supplemental analysis of PFS by blinded independent central reviewers was consistent with the primary investigator assessment (48).

Other studies on the role of PARPi as maintenance therapy after first-line chemotherapy are currently ongoing (Table VI).

The NCT04227522 MAMOC trial is a randomized phase III study including *BRCA*-non mutated patients with stage III-IV ovarian high-grade serous or high-grade endometrioid or clear cell carcinoma who have undergone BEV maintenance following first-line chemotherapy. After BEV treatment the patients will be randomized to receive either 600 mg rucaparib daily or placebo daily for 12 to 15 months.

NCT04532645 trial is a retrospective, non-interventional, observational cohort study of *BRCA*-mutated stage III-IV ovarian carcinoma patients treated with olaparib in the first-line maintenance setting in France, Italy, and UK. Physicians will be requested to recruit patients to have their clinical data abstracted from their clinical records in agreement with local laws.

The MITO 25 trial is a randomized, open-label Phase 1-2 study aimed to assess the effect of CBDCA + PTX + BEV (in combination and maintenance) *versus* CBDCA + PTX + BEV + Rucaparib (Rucaparib only in maintenance) *versus* CBDCA + PTX + Rucaparib (Rucaparib only in maintenance) on PFS of patients with advanced high grade ovarian carcinoma treated according to HRD status.

Trials With Immunotherapy

Up to now literature data suggest that the immune checkpoint inhibitors avelumab and atezolizumab have limited impact on the clinical outcome of patients with newly diagnosed ovarian carcinoma (49, 50) (Table VII).

The phase III NCT02718417 JAVELIN Ovarian 100 trial randomized 998 patients with stage III-IV ovarian carcinoma (after PDS or candidates to NACT) to receive PTX (175 mg/m^2 Q3W or 80 mg/m^2 weekly) + CBDCA AUC5-6 Q3W for 6 cycles followed by avelumab maintenance [10 mg/kg every 2 weeks (Q2W)] or the same chemotherapy concomitant with avelumab (10 mg/kg Q3W) followed by avelumab Q2W maintenance, or the same chemotherapy followed by observation (control arm) (49). At interim analysis PFS of both avelumab arms was not improved compared with the control arm, and the trial was stopped early.

The phase III trial NCT03038100 IMagyn050 randomly assigned 1301 stage III-IV ovarian carcinoma patients (with either macroscopic RD after PDS or candidates for NACT) to receive either atezolizumab (1,200 mg Q3W, cycles 1-22) or placebo (Q3W, cycles 1-22) combined with PTX (175 mg/m^2 Q3W, cycles 1-6) + CBDCA (AUC 6 Q3W cycles 1-6) + BEV (15 mg/kg Q3W, cycles 2-22) (50). Programmed death-ligand 1 (PD-L1) status [PD-L1–expressing immune cells (ICs) as percentage of tumor in <1% *versus* ≥1% (PD-L1–positive)] was assessed with immunohistochemistry (VENTANA). Atezolizumab failed to improve PFS both in intention to treat population and in patients with PD-L1–positive tumors. However, in a prespecified exploratory analysis with a threshold of PD-L1 IC ≥5% (representing 20% of the intention to treat population in the IMagyn050 trial), PFS was better in atezolizumab arm (median, not reached *versus* 20.2 months, HR=0.64, 95%CI=0.43-0.96). However, some trials investigating other immunotherapies in first-line treatment of advanced ovarian carcinoma are currently ongoing.

The purpose of the NCT03740165 ENGOT-ov43 trial is to assess the efficacy and safety of PTX + CBDCA ± pembrolizumab and maintenance olaparib in patients without *BRCA* mutations. Following a lead-in period during which all participants receive a single Q3W cycle of PTX + CBDCA, the patients are randomly assigned to chemotherapy + pembrolizumab followed by olaparib maintenance, chemotherapy + pembrolizumab followed by placebo maintenance or chemotherapy + placebo followed by placebo maintenance. All participants can also receive BEV on Day 1 of each Q3W cycle at investigator's discretion.

The NCT03522246 ATHENA, double-blind, dual placebo-controlled, 4-arm study is evaluating rucaparib and nivolumab as maintenance treatment following response to first-line chemotherapy. Response to treatment will be assessed according to HRD status. The 3 experimental arms are represented by rucaparib + nivolumab, rucaparib + intravenous placebo, oral placebo + nivolumab, whereas the control arm consists of oral placebo + intravenous placebo.

The NCT03275506A GINECO phase II trial randomized in a ratio 2:1 91 patients with unresectable stage IIIC-IV high-grade serous ovarian carcinoma to receive 4 cycles of PTX + CBDCA with or without pembrolizumab (51). Eighty of these patients also received BEV concurrently with chemotherapy and sequentially as maintenance with or without pembrolizumab. Complete resection at IDS was obtained in 71% and 58% of the patients treated with and without pembrolizumab, respectively. Survival data and translational research including PD-L1 status are ongoing to better define the role of pembrolizumab as treatment option in this clinical setting.

Gemogenovatucel-T is an autologous tumor cell vaccine obtained from harvested tumor tissue and genetically modified to express the granulocyte macrophage colony stimulating factor (GM-CSF) and to block the production of trasforming growth factor (TGF) TGF-β2 (52). NCT02346747 is a double-blind, placebo-controlled, phase 2b trial comparing this immunotherapy *versus* placebo as maintenance treatment in patients with advanced ovarian high-grade serous, endometrioid

or clear cell carcinoma in complete response after PDS and 5-8 cycles of PTX/CBDCA-based chemotherapy. Vaccine or placebo was administered intradermally every month for 4-12 doses (53). The preliminary assessment of 135 patients showed that the vaccine was associated with a trend to a better PFS (HR=0.69, 90%CI=0.44-1.07) in the whole population and a significantly better PFS in *BRCA*-wild type patients (HR=0.51, 90%CI=0.30-0.88). At a post-hoc analysis Gemogenovatucel significantly improved PFS (HR=0.386, 90%CI=0.199-0.750) and OS (HR=0.342 ,90%CI=0.141-0.832) in patients with HRP based on myChoice assay (score <42) (54).

Conclusion

The patients start chemotherapy with the first cycle of PTX (175 mg/m^2) + CBDCA (AUC5) Q3W regimen. The results of *BRCA* testing on tissue samples collected at PDS or laparoscopy or diagnostic imaging techniques guided biopsies should be available before the second cycle of chemotherapy. If *BRCA* is mutated, 5 cycles of PTX/CBDCA are administered and followed by olaparib maintenance in responsive cases according to SOLO-1 trial. Niraparib maintenance may represent an alternative option to olaparib maintenance. If *BRCA* is wild-type, the clinical behavior depends on both the availability of HRD assay as well as by the presence or lack of risk factors for BEV-related adverse events. These are represented by uncontrolled hypertension, clinically significant, cardiovascular disease, non–healing wound, thrombotic or hemorrhagic disorders (including cerebrovascular accident/stroke or transient ischemic attack or sub-arachnoid haemorrhage), signs or symptoms of gastrointestinal obstruction or history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the preceding 6 months.

HRD assay not available.
i) No contraindications to BEV: BEV can be added concurrently to PTX/CBDCA and then sequentially as maintenance therapy according to GOG 218 trial. Patients who undergo IDS omit both perioperative cycles of BEV.
ii) Contraindications to BEV: PTX/CBDCA regimen is continued and then followed by niraparib maintenance in responsive cases, especially in patients with stage III disease with visible RD after PDS, inoperable stage III disease, stage IV disease and in patients who had received NACT. In the PRIMA trial niraparib has offered a median absolute PFS benefit of 5.6 months (HR=0.62) compared with placebo in the intention to treat population.

HRD assay positive
i) No contraindications to BEV: BEV can be added concurrently to PTX/CBDCA and then sequentially and olaparib can be added as maintenance therapy in responsive cases according to the PAOLA-1 trial. Patients who undergo IDS omit both perioperative cycles of BEV. In the PAOLA-1 study olaparib + BEV has been associated with a median absolute PFS advantage of 11.5 months (HR=0.43) *versus* placebo + BEV in patients with HRD tumor and *BRCA*-wt.
ii) Contraindications to BEV: PTX/CBDCA regimen is continued and then followed by niraparib maintenance in responsive cases, especially in patients with stage III disease with visible RD after PDS, inoperable stage III disease, stage IV disease and in patients who had received NACT. In the PRIMA trial niraparib has given an absolute median PFS benefit of 11.4 months (HR=0.50) compared with placebo in patients with HRD tumor and *BRCA*-wt.

HRD test negative.
i) No contraindications to BEV: BEV can be added concurrently to PTX/CBDCA and then sequentially as maintenance therapy according to the GOG218 trial. Patients who undergo IDS omit both perioperative cycles of BEV.
i) Contraindications to BEV: PTX/CBDCA regimen is continued and eventually followed by niraparib maintenance in responsive cases especially in patients with stage III disease with visible RD after PDS, inoperable stage III disease, stage IV disease and in patients who had received NACT. In the PRIMA trial niraparib has significantly improved PFS (HR=0.68) compared with placebo in patients with HRP tumor, with an absolute median PFS benefit of only 2.7 months.

The role of immunotherapy in first-line treatment of newly diagnosed ovarian carcinoma is still investigational.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, Writing - original draft: Angiolo Gadducci; Data curation, formal analysis, methodology, writing, review and editing: Angiolo Gadducci and Stefania Cosio.

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