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Anti-angiogenic therapy for ovarian cancer

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ABSTRACT

Angiogenesis is a known hallmark in cancer and plays a crucial role in ovarian cancer carcinogenesis and invasion. Anti- angiogenic agents are active in ovarian cancer treatment either as monotherapy or combined with chemotherapy, immunotherapy or poly ADP ribose polymerase (PARP) inhibitors. We review the mechanism of action, clinical activity and safety profile of the most important drugs either in the actual treatment or in current evaluation in the ovarian cancer treatment scenario (neoadjuvant, first line and relapse).

1. Anti-angiogenic therapy for ovarian cancer

Angiogenesis plays a key role in ovarian cancer progression allowing tumour invasion and metastasis and is known to be essential for tumour growth beyond 1–2 mm[1]. Vascular endothelial growth factor (VEGF) is the main factor of angiogenesis in solid tumours, with its binding to VEFGR-1/2 receptors in target cells, that initiates a signalling cascade by intracellular tyrosine kinases. It promotes the recruitment of endothelial cell progenitors of the bone marrow, their survival and differentiation[2]. In addition, other growth factors are involved, such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and angiopoietin 1 and 2. These factors bind to different receptors, each one transmitting its intracellular signals through a different set of tyrosine kinases [3] (see Tables 1 and 2).

Several drugs have been developed to target all these signalling pathways involved in the angiogenesis process. These are known as anti-angiogenic (AAs) drugs, among them, we include humanised anti-VEGF monoclonal antibodies, such as bevacizumab, soluble VEGFR, such as aflibercept; peptide/antibody fusion proteins, such as trebananib, and small molecule tyrosine kinase inhibitors (TKI), such as cediranib, pazopanib, sunitinib and nintedanib [1]. We present a thorough review of these drugs.

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2. Bevacizumab

Bevacizumab is a humanised monoclonal IgG antibody that targets vascular epithelial growth factor (VEGF A) and is the most studied anti-angiogenic agent in ovarian cancer. It has proven its effectiveness as a single agent in platinum-resistant ovarian cancer and in combination with chemotherapy in the adjuvant setting and recurrent disease and has recently been tested in the neoadjuvant setting.

2.1. *Front-line therapy*

To date, two randomized double-blind phase III trials have given the approval for bevacizumab in the adjuvant setting.

In GOG-0218 [4], 1873 women with stage III (74%) and IV (26%) ovarian cancer (OC) were treated in a three-arm, placebo-controlled study. Forty per cent of the patients had macroscopic residual disease. They were randomised to receive standard chemotherapy (CT) with 3-weekly carboplatin-paclitaxel with either placebo or bevacizumab (15 mg/kg/3w) concurrently and also as maintenance treatment for up to 16 doses in a three-arm trial with placebo during CT and in maintenance, CT with bevacizumab (15 mg/kg/3w) and placebo maintenance (bevacizumab-initiation) and CT + bev and bev maintenance for up to 16 doses (bevacizumab throughout), chemotherapy; 19% completed the planned treatment. The primary end-point was progression-free survival (PFS) that was longer in the bevacizumab initiation arm (HR 0.908; $p = 0.16$; median 11.2 versus 10.3 months) and significantly longer in the bevacizumab throughout arm (HR 0.717; $p < 0.001$; median 14.1 versus 10.3 months). This difference in terms of efficacy was consistent across all patients subgroups stratified. No significant differences in overall survival (OS) among the three arms were identified. Hypertension grade$\geq$2 was higher in the bevacizumab arm: 16.5% in bevacizumab initiation, 22.9% in bevacizumab throughout and 7-2% in the control arm. There was no difference between groups regarding proteinuria, neutropenia, wound disruption or gastrointestinal perforation. A final OS analysis has been published. With a median follow up-of 102.9 months, the previous data reported showing no benefit in PFS, DFS or OS was confirmed as was the benefit in OS in the high-risk stage IV subgroup for the bevacizumab maintenance, 42.8 versus 32.6 months for stage IV control (HR, 0.75; 95% CI, 0.59 to 0.95) [5].

ICON7[6] was the second phase III trial that evaluated this aspect. It was a two-armed randomized phase III trial comparing CT (carboplatin + paclitaxel) against CT and maintenance with bevacizumab (7.5 mg/kg/3w). A total of 1528 women with high-risk disease: stages I-IIa disease (grade 3 or clear cell histology) (9%) or more advanced disease stages IIb-IV (91%) after debulking surgery, were enrolled. There was significant improvement in PFS, which was the primary end-point of the study, in the bevacizumab arm (HR 0.81; $p = 0{,}004$; median 19 versus 17.3 months). In the subgroup of patients at high risk of recurrence (stage IV and stage III with residual disease >1 cm), the benefit of bevacizumab was more pronounced, with a 5.4 -month improvement in PFS, and it was similar to that found in the high-risk GOG218 group. The final analysis of mature OS data showed no difference between arms (HR 0.99; $p = 0.89$; 58.6 versus 58.0 m)[7]. Interestingly, the beneficial effects of bevacizumab in the subset of patients at high risk for progression continued (HR = 0.78, $p = 0.01$; 30-2 versus 39-7 m). A subset of patients who might not benefit from bevacizumab was also identified: women with early-stage and/or with optimally debulked (<1 cm) stage III. These finding are relevant since, in practice, bevacizumab is used based on the risk and disease burden. The adverse events observed in this study were comparable to those seen in GOG-0218 (toxicity table).

A prospective, observational, phase IV study, OTILIA[8] completed recruitment in September 2019, and final results are pending. The aim of this trial is to assess the safety and effectiveness of front-line bevacizumab-containing therapy in the real-world setting. Preliminary results suggest that the activity and tolerability observed in randomized trials appear to be reproducible in daily practice. The average time of bevacizumab therapy was 14.0 m (95%CI 13-4-14-3 m). The reasons for discontinuation were disease progression (31%), side-effects (15%) and patient's request (8%). Median PFS was 21.7 m (95% CI 20.7–22 m). Elderly patients >70 years benefited as much as younger patients. In terms of safety, there was no difference between patients aged <70 versus $\geq$70 years regarding median PFS; 27% of patients presented grade $\geq$3 adverse events, and this led to bevacizumab discontinuation in 5% of the sample. The incidence of all-grade hypertension, proteinuria and gastrointestinal perforation was 11%, 2% and 0.8%, respectively, and there was similar tolerability in subgroups stratified by age.

Moving forward to important questions about bevacizumab use in daily practice, The MITO16/MANGO2b trial assessed the treatment beyond progression issue. In this trial, 405 patients with recurrent ovarian cancer >6 months after completion of first-line chemotherapy and in which bevacizumab was already used in first-line treatment, were included and randomized to platinum doublet chemotherapy with or without bevacizumab. Sixty-four percent of the patients had a >12-month recurrence and 72% completed the full-length bevacizumab treatment in first line. The results favoured the experimental arm in the primary objective, PFS, with 11.1 versus 8.8 months (HR 0.51, 95%CI: 0.41–0.64, $p < 0.001$) and no different safety profile was detected[9,10].

Another important question still unanswered is the optimal duration of bevacizumab in front-line treatment. Bevacizumab treatment with 15 versus 30 months length is being explored n the BOOST trial (NCT01462890).

2.2. *Recurrent disease*

Bevacizumab has also shown efficacy in the recurrent setting as monotherapy in the initial phase II trials and in platinum-sensitive and platinum-resistant disease. The OCEANS[11,12] study is a blinded, placebo-controlled phase III trial, that randomizes a total of 484 women with platinum-sensitive recurrent ovarian cancer to receive CT (carboplatin + gemcitabine) plus placebo or CT plus bevacizumab (15 mg/kg) until progression. Patients were stratified in platinum-free interval (PFI) (6–12 versus >12 m) and cyto-reductive surgery for recurrent disease (yes versus no).

Table 1 – Phase III studies with anti-angiogenic drugs in ovarian cancer.

Study	N	Setting	Eligibility	Regimen	Median PFS (months)	OS (m)	RR
GOG-0218	1873	Adjuvant	OC, stages III-IV, macroscopic residual disease after debulking surgery	6 cycles CP or CP + bevacizumab 15 mg/kg with or without maintenance with bevacizumab	[a]10.3 versus 11.2 HR 0.908 P = 0.16Maintenance with bevacizumab 10.3 versus 14.1 HR 0.717 P < 0.001	36.3 versus 38.7 HR 1.036 P = 0.76Maintenance with bevacizumab 39.3 versus 39.7 HR0.915 P = 0.45	X
ICON 7	1528	Adjuvant	OC, stages I-IIa with high risk disease and stages IIb-IV after debulking surgery	6 cycles CP or CP ++ bevacizumab 7.5 mg/kg and maintenance with bevacizumab	[a]17.3 versus 19 HR 0.8 p = 0.004	58 versus 58.6 HR = 0.99 p = 0.89	48% versus 67% p < 0.001
OCEANS	484	Recurrent platinum sensitive	Relapsed platinum-sensitive OC, up to platinum-based chemotherapy	CG + placebo versus CG ++ bevacizumab 15 mg/kg and maintenance with bevacizumab	[a]8.4 versus 12.4 HR = 0.484 p < 0.0001	32.9 versus 33.6 HR = 0.95 p = 0.65	57.4% versus 78.5% p < 0.0001
GOG-0213	674	Recurrent platinum sensitive	Relapsed platinum sensitive OC, up to platinum-based chemotherapy	CP or CP + bevacizumab 15 mg/kg with maintenance with bevacizumab	[a]10.4 versus 13.8 HR = 0.628 p < 0.0001	37.3 versus 42.2 HR = 0.829 p = 0.056	59% versus 32% p < 0.0001
AURELIA	361	Recurrent platinum resistant	Relapse platinum- resistant OC, up to platinum-based chemotherapy	Standard chemotherapy (PDL, Top, weekly P) + or standard chemotherapy + bevacizumab 15 mg/kg	[a]3.4 versus 6.7 HR = 0.4 p < 0.001	13.3 versus 16.6 HR = 0.85 p = 0.174	12.6 versus 30.9 p = 0.001
AGO-OVAR-16	940	Maintenance therapy	OC, stages II-IV, with no progression after primary surgery and at least 5 cycles of platinum-taxane	pazopanib 800 mg daily or placebo, 24 m	[a]17.9 versus 12.3 HR 0.77; p = 0.0021	X	NR
AGO-OVAR-12	1366	Adjuvant	OC, stages IIB-IV, chemotherapy-naive and upfront debulking surgery	6 cycles of CP ++ 200 mg of nintedanib or placebo twice daily up, days 2–21 of every 3-week cycle up to 120 weeks	[a]17.2 versus 16.6 HR 0.84; p = 0.024	NR	NR
ICON 6	456	Recurrent platinum sensitive and maintenance	Relapsed platinum-sensitive OC, up to 6 cycles of platinum-based chemotherapy then entered a maintenance phase	Placebo + CT and placebo maintenance (arm A), cediranib 20 mg once-daily + CT and placebo maintenance (arm B), or cediranib 20 mg once-daily + CT then cediranib maintenance (arm C)	[a]11.0 versus 8.7 HR 0.56 p < 0.0001 (arm C versus A) 9.9 (arm B)	X	NR
TRINOVA-1	919	Metastatic	≤3 regimens, and a platinum-free interval of <12 m	weekly intravenous paclitaxel (80 mg/m^2) + either weekly placebo or trebananib (15 mg/kg)	[a]7,2 versus 5,4 HR 0.66, p < 0.0001	X	29.8% versus 38.4% p = 0.03
TRINOVA-2	223	Recurrent Platinum sensitive	Recurrent OC (platinum-free interval ≤12 m)	PLD 50 mg/m^2 4 weeks + weekly intravenous trebananib 15 mg/kg or placebo	X	X	46% versus. 21%; p < 0.001

C = carboplatin, P = paclitaxel, G = gemcitabine, PLD = pegylated liposomal doxorubicin, Top = topotecan.
[a] Primary end-point.

Table 2 – angiogenic drugs adverse events among FIII studies.

Drug	HTA	Thrombo-embolic events A/V	Intestinal Perforation	Proteinu-ria	Fatigue	Neutropenia	Anaemia	Thrombocytopenia	Diarrhoea	Oedema	Palmoplantar erythrodysesthesia
Bevacizu-mab[4-13]	Any grade: 26% G3/4: 6–17.8%	Any grade: 11% G3/4: 0.7–6.7%	G3/4: 0–2.2%	Any grade: 14% G3/4: 0.7–9.7%	NR	Any grade: 29% G3/4: 17–63.3%	NR	Any grade: 12% G3-4: 3–12%	NR	NR	NR
Pazopanib[17,18]	Any grade: 5.77% G3/4: 30.8%	NR	NR	Any grade: 8.4% G3/4:1.3%	Any grade 41.5% G3/4:2.7%	Any grade: 31.7% G3/4: 9.9%	NR	Any grade: 15.8% G3/4:2.5%	Any grade: 53% G3/4: 8.2%	NR	Any grade:13.4% G3/4: 1.9%
Nintedanib[14.15]	Any grade 15% G3/4: 5%	Any grade: 8% G3/4: 5%	Any grade 4% G3/4: 2%	NR	Any grade: 59% G3/4: 7%	Any grade: 33% G3/4: 20%	Any grade: 43% G3/4: 13%	Any grade: 38% G3/4: 18%	Any grade: 77% G3/3: 22%	NR	NR
Cediranib[20,22]	Any grade: 35–45% G3/4: 5–12%	Any grade: 5% G3/4: 3%	G3/4: <1%	Any grade: 18% G3/4: 1%	Any grade: 77–79% G3/4: 6–16%	Any grade: 29–69% G3/4: 6–26%	NR	Any grade: 27–47% G3/4: 2–8%	Any grade: 86–92% G3/4 : 1–11%	NR	NR
Trebananib[16,19]	Any grade: 11% G3/4 1%	<2%	<2%	<2%	Any grade: 24–57% G3/4: 3%	Any grade: 16% G3/4: 5%	Any grade: 9–10% G3/4: 1%	NR	Any grade: 27% G3/4: 2%	Any grade: 61–71% G3/4: 19–21%	Any grade: 69% G3/4: 22%

NR = not reported.

Interestingly, the addition of bevacizumab conferred a significant improvement in PFS (HR = 0.48, p = 0.001; 12.4 versus 8.4 months) and was also associated with a higher objective response rate (ORR) (78.5% versus 57.4%; p < 0.001) and prolonged the duration of response (HR = 0.534, 10.4 versus 7.4 m). The final analysis of mature OS data showed no difference between arms (HR 0.95; p = 0.65; 33.6 versus 32.9 m). Regarding toxicity, grade 3 or higher hypertension and proteinuria occurred more frequently in the bevacizumab arm. No cases of gastrointestinal perforation occurred during the study or within the 30-day reporting period. The rates of neutropenia and febrile neutropenia were similar in both arms.

The GOG-0213 trial[13] is another recent phase III study that was performed in recurrent platinum-sensitive disease. The primary objective of this study was twofold: bevacizumab efficacy in the recurrent scenario and the role of secondary cytoreduction surgery before the initiation of chemotherapy (surgical objective is accruing). A total of 674 women were randomized to standard chemotherapy or chemotherapy plus bevacizumab (15 mg/kg). It showed a non-statistically significant OS advantage of 42.3% versus 37.2% against bevacizumab (HR = 0.829, p = 0.056), but a post-hoc sensitivity analysis adjusted HR = 0.823, p = 0.0447. Bevacizumab also showed an improved in PFS of 13.8 versus 10.4 months (HR 0.628, p < 0.0001). OR was also higher in the bevacizumab arm, 78% and 59% (p < 0.0001), with higher CR including a greater number of patients who achieved a complete response: 32% versus 18%. The adverse events were consistent with the known safety profile of the agents under study.

The AURELIA trial[14,15] **is the main study performed** in the platinum-resistant setting. This is a randomized open-label phase III clinical trial that evaluates the addition of bevacizumab to standard chemotherapy (topotecan, PDL or weekly paclitaxel) in patients with disease progression <6 m after completion of front-line platinum-based chemotherapy). Overall, 361 women were included, and crossover was permitted. Median PFS was longer in the bevacizumab arm (HR = 0.48, p < 0.001, 16.6 versus 13.3 m) and was significantly longer in patients who received paclitaxel + bevacizumab (HR = 0.65, 22.4 versus 13.2 m). The study was not powered to detect statistically significant differences in OS. The authors of the trial described higher rates of grade ≥3 hypertension (7% versus 1%) and proteinuria (8.5% versus 0.9%) in the experimental arm. It is worth mentioning that gastrointestinal perforation occurred in 2.2% of bevacizumab-treated patients.

2.3. *Neoadjuvant setting*

Finally, the neoadjuvant setting has been explored through two phase II randomized trials: the ANTHALYA and the NOVA-GEICO 1205 trials[16,17].

The primary objective of the ANTHALYA trial was to assess whether adding bevacizumab to CT would improve the complete resection rate at interval debulking surgery. On the one hand, the ANTHALYA trial is an open-label, non-comparative, phase II study, whose primary objective is to improve optimal debulking measured as resection rate. The study included 95 women in a 2:1 randomization and found a total of 95 women were randomized (2:1) to receive chemotherapy for 4 cycles with or without bevacizumab (15 mg/kg) concomitantly for 3 cycles, and adjuvant treatment with chemotherapy plus bevacizumab for 4 cycles and maintenance with bevacizumab up to 26 cycles. The complete resection rate was higher R0 resection in the experimental arm (58.6% versus 51.4%). Surprisingly, non-significant differences were found in grade ≥3 adverse events between groups, with 62% of patients presenting AEs in the control arm versus 63% in the bevacizumab arm. Furthermore, postoperative complications (mainly wound, infectious and gastrointestinal complications) occurred in 28% versus 36%, respectively[16].

The NOVA-GEICO 1205 trial was a phase II open-label study that evaluated NA bevacizumab in 68 patients in a 1:1 randomization. No differences in complete macroscopic rate (primary objective) or PFS were found. Although surgical feasibility was improved in the NA arm (67 versus 89%; p = 0.029), there were no differences in R0 resections. Safety favoured the bevacizumab arm with less ≥ grade 3 events, during the whole treatment period (79 versus 54%, p = 0.033) and in the NA period (61 versus 29%, p = 0.008). These results suggest that bevacizumab may be safely added to a preoperative programme in patients with initially unresectable disease, without increasing the incidence of postoperative complications. However, the role of bevacizumab in this setting must be further investigated[17].

3. Pazopanib

Pazopanib is an oral TKI which inhibits VEGFR, PDGFR and cKit signalling. Based on the promising results of a phase II study [18], a double-blind, placebo-controlled, randomized, phase III study, AGO-OVAR16, evaluated the benefit of maintenance treatment with pazopanib in patients with advanced OC treated with front-line chemotherapy after debulking surgery [19]. Patients with persistent bulky disease after surgery were excluded from this study. A total of 940 patients with histologically confirmed OC, stages II-IV, with no evidence of progression after primary surgery and at least five cycles of platinum-taxane-based chemotherapy, were randomized 1:1 to receive pazopanib 800 mg once per day or placebo for up to 24 months. Patients were stratified by first-line treatment outcome and geographic region. Maintenance pazopanib showed an increase in PFS compared with placebo, HR 0.77; p = 0.0021; median 17.9 versus 12.3 m, respectively, but the study was closed due to futility after a third interim analysis in 86% of OS events with no significant differences. One important point to mention about this study is that more than half of the patients included had no residual disease after surgery (58%) and most patients (88%) were free of disease at study entry. Grade 3 or 4 adverse events of hypertension (30.8%), neutropenia (9.9%), liver-related toxicity (9.4%), diarrhoea (8.2%), fatigue (2.7%), thrombocytopenia (2.5%), and palmar-plantar erythrodysesthesia (1.9%) were significantly higher in the pazopanib arm. Finally, in Asian patients, the dose of pazopanib was reduced from 800 mg to 600 mg daily due to side-effects and a trend to better OS in placebo-treated patients was noticed.

4. Nintedanib

Nintedanib is an oral triple inhibitor of VEGF receptor, PDGF receptor and basic fibroblast growth factor (bFGF). In a phase II study[20], nintedanib showed a PFS advantage of 16.3% versus 5% against placebo, when administered to patients with ovarian cancer as a maintenance treatment after their last chemotherapy. AGO-OVAR 12 [21,22], a double-blind, placebo-controlled, phase III study, evaluated the benefit of adding nintedanib to standard front-line treatment, carboplatin and paclitaxel, after debulking surgery in patients with OC, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stages IIB–IV. The primary end-point was PFS, which was significantly longer in the nintedanib group than in the placebo group, 17.2 m versus 16.6 m, HR 0.84; $p = 0.024$. Although in a preplanned subgroup analysis, PFS was initially reported to be improved in the nintedanib group compared with the placebo group for patients with stages IIB–III disease, those differences were not confirmed in the final report, and no significant differences were noted in subgroups according to the presence of macroscopic residual tumour.

In a post-hoc analysis, the non-high-risk subgroup defined as the International Federation of Gynecology and Obstetrics (FIGO) stage III and postoperative residual disease of 1 cm or smaller, or FIGO stage II, showed a PFS advantage of 27.1 m in patients in the nintedanib group versus 20.8 m in those in the placebo group (HR 0.74). No significant differences in PFS were observed between the nintedanib and placebo groups for high-risk subgroup (HR 0.99).

These findings seem to differ from the outcome of trials with bevacizumab, which show an evidence of both PFS and OS benefit, but only for patients with high-risk features or a high postsurgical tumour burden. Inclusion criteria were similar between AGO-OVAR 12 and ICON7. In contrast, the results of AGO-OVAR 12 are in line with the findings for pazopanib in the AGO-OVAR 16 phase 2 study.

The most common adverse events described in this study were gastrointestinal with 21% of patients in the nintedanib group presenting diarrhoea grade 3 against 2% in the placebo group and 22% haematological; with 20% of patients presenting grade 4 neutropenia in the nintedanib group against 16% in the placebo group.

5. Trebananib

Trebananib, also called AMG 386, is a peptide-Fc fusion protein that prevents the activation of the TIE2 receptor by angiopoietin 1 and 2. Angiopoietin 1 is involved in the stabilisation of endothelial junctions, while angiopoietin 2 promotes endothelial sprouting; these ligands increase blood vessel density. The double-blind, placebo-controlled, phase III, TRINOVA-1 study[23], evaluated the addition of trebananib to single-agent weekly paclitaxel in patients with recurrent EOC. Patients were stratified by platinum-free interval (PFI) ($\geq$0 and $\leq$6 m versus >6 and $\leq$ 12 m), measurable disease, and region. Median PFS was significantly longer in the trebananib group than in the placebo group: 7.2 m versus 5.4 m, respectively, HR 0.66, $p < 0.0001$). In subgroup analysis, treatment effect did not seem to be affected by the number of previous regimens or by PFI. Objective responses (ORs) were significantly more frequent with trebananib than with placebo, 30% versus 38%, respectively. The interim OS analysis did not show any significant difference between groups.

This is the only randomized trial, together with AURELIA, that showed a significant improvement in PFS in platinum-resistant patients.

The double-blind, placebo-controlled, phase III study ENGOT-OV-6/TRINOVA-2 [24] evaluated whether trebananib plus pegylated liposomal doxorubicin (PLD) improved progression-free survival (PFS) in patients with recurrent epithelial ovarian cancer (EOC). Eligible patients had received one prior platinum-based chemotherapeutic regimen with a platinum-free interval (PFI) of 12 m and could have received 2 additional cytotoxic regimens for recurrent/persistent disease. Patients were randomized to intravenous PLD 50 mg/m^2 once every 4 weeks plus weekly intravenous trebananib 15 mg/kg or placebo. Median PFS was not significantly improved, 7.6 m in the trebananib group and 7.2 m in the placebo group. Conversely, ORR was significantly higher in the trebananib group against placebo, 46% versus 21%.

In both trials, trebananib was associated with an increased rate of localised oedema in comparison with placebo, including ascites and pleural effusions. Conversely, there was a non-significant difference in class-specific adverse events associated with anti-VEGF therapy.

In favour of this study, we could argue that the use of non-platinum chemotherapy might be a valuable treatment option for patients with partially platinum-sensitive disease. Response to platinum-containing recurrence therapy varies among this patient subgroup. Additionally, some patients might not be eligible to receive a platinum doublet as recurrence treatment for various reasons.

Unfortunately, enrolment was temporarily halted for 14 months in the TRINOVA-2 trial, due to pegylated liposomal doxorubicin shortage in certain regions. This may have affected the final results of the study, although another phase III study, TRINOVA-3 (NCT01493505), that evaluated the efficacy of combining trebananib with first-line carboplatin and paclitaxel in patients with EOC, stages III-IV, was prematurely terminated by decision of founder given the disappointing results of prior trials and toxicity profile.

6. Cediranib

Cediranib is a potent oral inhibitor of all 3 VEGFR tyrosine kinases (VEGFR1, 2, 3), with 800–5000 fold selectivity for the VEGFR2 and c-Kit inhibitor. A Phase II study evaluated cediranib (30 mg daily) as a single agent for recurrent EOC, with 30% of patients presenting clinical benefit, 17% partial responses (PRs) and 13% stable disease (SD)[25]. On the basis of the phase 2 activity in ovarian cancer, a phase III, three-arm, double-blind, ICON-6 study [26] assessed efficacy and safety of cediranib in combination with platinum-based chemotherapy and as a maintenance treatment in patients who had radiological evidence of recurrence more than 6 months after completion of first-line chemotherapy. This trial was prematurely terminated due to a decision by AstraZeneca to

discontinue cediranib development in October 2011, after disappointing outcomes from pivotal trials in other tumour types. The primary end-point was subsequently changed to PFS and the trial consequently was underpowered for OS. A total of 456 women were randomized 2:3:3, with five stratification factors and in alternating blocks, to receive placebo alongside chemotherapy followed by placebo-only maintenance (arm A; reference), cediranib 20 mg once daily alongside chemotherapy then placebo-only maintenance (arm B; concurrent), or cediranib 20 mg once daily alongside chemotherapy then cediranib 20 mg once daily maintenance (arm C; maintenance). Median PFS was 11.0min arm C, and 8.7 m in arm A (HR 0.56; $p < 0.0001$). Median PFS in arm B was 9.9 m.

The preliminary OS results with 52% of the events at cut-off showed no statistically significant differences in median OS between arm C and A (26.3 m versus 21 m (HR 0.77; $p = 0.11$). Updated OS results were presented at the American Society of Clinical Oncology (ASCO) 2017, after a median follow-up of 25.6 m with 86% of the events at cut-off, the median OS was 19.9 m for patients in arm A and 27.3 m for those in arm C (HR 0.85; $p = 0.21$) this translates into a median difference of 7.4 m.

Diarrhoea, neutropenia, hypertension and voice changes were significantly more common during chemotherapy with cediranib, and diarrhoea, hypothyroidism and voice changes were more common during maintenance. Poor compliance with cediranib was noted during maintenance treatment with toxic effects being the most common cause for discontinuation.

7. Other anti-angiogenic agents

The efficacy of other AA in OC has been also evaluated:

Sunitinib is a multi-targeted TKI, which was evaluated in a phase II study as monotherapy in patients with recurrent OC treated with one or two previous lines[27]. A total of 73 patients were given sunitinib to 50 mg intermittently (4 weeks on and 2 weeks rest) or 37.5 mg continuously. An RR of 5.4% was observed with PFS of 2.9 and OS of 13.7 m. Moreover, another phase II study evaluating this setting was performed. Thirty-five patients with recurrent OC were given sunitinib with monotherapy in a daily dose of 37.5 mg in a 28-day-cycle. An RR of 8.3% was obtained, with PFS of 9.9 weeks. No OS analysis was reported.

Sorafenib is also a small molecule TKI of several tyrosine protein kinases, such as VEGFR, PDGFR. In a phase II study, it has been tested in the neoadjuvant setting in combination with carboplatin-paclitaxel in a daily dose of 400 mg, in patients with advanced stages and large ascites volume[28]. Unfortunately, the study was closed after enrolling only 4 patients due to life-threatening toxicities. In another placebo-controlled phase II study, its efficacy was evaluated in monotherapy as a maintenance treatment after complete remission with first-line treatment[29]. No differences in PFS were found against placebo (12.7 versus 15.7 months). More G3 toxicities were observed with sorafenib than with placebo. Finally, its combination with bevacizumab was evaluated in another phase II study, in patients who had not been treated with the monoclonal antibody. It showed a clinical benefit of 85% with 16/25 PR and 16/35 SD for more than 4 months[30].

Aflibercept is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF)-binding portions from the extracellular domains of human VEGF receptors 1 and 2, that are fused to the Fc portion of the human IgG1 immunoglobulin. To date, its activity in ovarian cancer has been evaluated in several phase II trials. One phase II study combined aflibercept at 6 mg/kg with docetaxel 75mg/m2 every 3 weeks showed an RR of 54% with 11 CR and 14 PR[31]. In another phase II trial, aflibercept was given at 4 mg/kg every 2 weeks to patients with recurrent epithelial ovarian cancer with symptomatic ascites that required 3 or more paracentesis[32]. The primary objective was to double the time to next paracentesis compared to the basal interval. A response was seen in 62.5% of patients with an average time to next paracentesis of 76 days compared to 16.8 days before starting aflibercept.

8. angiogenic treatment in combination with PARP inhibitors

PARP inhibitors have gained recent approval in ovarian cancer. They have different mechanisms of action such as blocking the functions of repair of PARP. It seems that hypoxia enhances PARP inhibition and simultaneously PARP inhibition reduces the pathway of angiogenesis driven by VEGF and increases the phosphorylation of VEFGR2. This has increased the interest in combining AA treatment, especially VEFGR2 inhibitors such as cediranib and PARP inhibitors. The combination of different chemotherapy-free regimens was tested, and results freed. Cediranib and olaparib have already been tested in a phase II study in patients with high-grade platinum-sensitive recurrent serous ovarian cancer[33]. The primary end-point was that PFS. 52% of patients were BRCA-mutated and 20% had received three or more treatment lines. Median PFS with olaparib alone versus cediranib plus olaparib was 17.7 and 9 m, respectively (HR 0.42; $p = 0.005$). ORR of 47.8% for olaparib and 76.6% olaparib plus cediranib were documented. Furthermore, a post-hoc analysis showed that OR and PFS increased with the combination in BRCA wild-type patients or in a population with unknown BReast CAncer gene (BRCA) with an average PFS of 5.7 m. An update of the results was presented at ASCO 2017 and recently published. An OS benefit in the BRCAwt subgroup, with 37.8 versus 23.7 months (HR: 0.44, 95%CI 0.19–1.01, $p = 0.047$) favouring the combination armEAs were more frequent with the combination (70% versus olaparib 7%): fatigue (27 versus 7%), diarrhoea (23 versus 0%), hypertension (39 versus 0%), respectively[34]. ICON 9 is a placebo-controlled phase III study in which patients in remission to 4–6 cycles of platinum-based chemotherapy are being randomized to maintenance with cediranib plus olaparib versus maintenance with cediranib plus placebo NCT03278717). Primary end-points are PFS and OS. Another phase III trial evaluating this strategy is the NRG GY004 trial which has completed accrual but results are pending (NCT02446600).

The AVANOVA2 study, a phase II randomized trial in BReast CAncer gene platinum-sensitive relapsed ovarian

cancer patients, tested niraparib in combination with bevacizumab versus niraparib monotherapy. In this study, the combination arm showed a benefit in PFS for the combination in the intent-to-treat (ITT) population with 11.9 months (95% CI 8.5–16.7) in the niraparib plus bevacizumab group versus 5.5 months (3.8–6.3) with niraparib, HR: 0.35 [95% CI 0.21–0.57], p < 0.0001). All HRD subgroups benefited and bevacizumab in previous lines was allowed and 21% in experimental and 27% control all the patients had received it previously[35]. This strategy is being evaluated in two important phase III trials, the FIRST study (NCT03602859), a phase III randomized trial in first line and the ANITA trial in platinum sensitive relapse (NCT03602859). Both trials incorporate bevacizumab in combination with chemotherapy and maintenance and evaluate the association with niraparib and an immune checkpoint inhibitor, dostarlimab in the FIRST trial and atezolizumab in the ANITA trial.

PAOLA1 is a phase III trial that included 806 patients in first line and allowed inclusion of newly diagnosed epithelial high-grade stage III-IV patients after surgery, either primary or interval, and chemotherapy (platinum–taxane) with bevacizumab. Patients were randomized to either olaparib or placebo. BRCA status was determined but all comers were included. Preliminary results reported in ESMO 2019 showed benefit for olaparib treated patients with 22.1 month in the olaparib arm versus 16.6 in the control arm, HR: 0.59 (0.49–0.72) p < 0.0001. As expected, the results were better in BRCA mutated and HRD positive patients for the olaparib arm. Interestingly, the proficient/not determined HRD group did not show any difference in terms of PFS in a post-hoc analysis. PFS2 and OS results are still immature[36].

Important ongoing phase III trials in first line setting such as DUO-O (NCT03737643) and ENGOT 43 (NCT03740165) evaluate different combinations with PARP inhibitors and immunocheckpoint inhibitors and bevacizumab is allowed as standard treatment and will add data about the benefit of combining different strategies.

9. angiogenic treatment and immunocheckpoint inhibitors

Although immunotherapy with either anti-PDL1 or anti-PD1 agents did not provide important clinical results with ORR around 10%, combination of anti-angiogenic agents and checkpoint inhibitors has a strong biological rationale that has led to the conduction of different clinical trials. DNA damage induced by AAs can contribute to the anti-tumour activity of immunocheckpoints[33]. PD-L1 expression is upregulated under hypoxic conditions through a hypoxia-inducible factor–dependent mechanism[34] and VEGF suppresses lymphocyte trafficking across endothelia into neoplastic deposits and sites of inflammation to promote vessel growth and reduces the anti-tumour immune response[37].

The currently ongoing Imagyn 050 (NCT03038100) trial is a phase III placebo controlled randomized trial in first line stage III-IV epithelial ovarian cancer patients that evaluates the addition of atezolizumab to chemotherapy and bevacizumab followed by bevacizumab and either atezo or placebo maintenance. The recruitment is completed and results are expected in late 2020.

10. Conclusions

Antiangiogenic treatment has demonstrated activity in different settings of OC. To date, eight phase 3 randomized controlled trials incorporating AA therapy in the treatment of newly diagnosed and recurrent ovarian carcinoma have met their primary end-points, most of them in terms of PFS. Four of these trials included bevacizumab and the other four studies were communicated, each studying one of the following novel anti-angiogenetic agents: pazopanib, cediranib, trebananib and nintedanib. Several other phase II trials have shown a certain activity of other AA drugs in terms of median PFS and RR.

Combinations with PARP inhibitors and immune-checkpoints due to synergic mechanism are presently being explored and seem to also have a potential role in recurrent and first line OC.

Nonetheless, the patterns of efficacy may differ between AA TKIs (nintedanib and pazopanib) and antibodies (bevacizumab) between high-risk and non-high-risk groups, given the outcomes of some phase III studies. However, this aspect must be further evaluated.

Conflict of interest statement

All the listed authors declare their conflict of interest:

María Marín Alcalá, MD: none.

Clara Martínez Vila, MD: none.

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Travel expenses: Roche, Lilly, Boehringer, BMS.

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REFERENCES

[1] Choi H-J, Armaiz Pena GN, Pradeep S, Cho MS, Coleman RL, Sood AK. Anti-vascular therapies in ovarian cancer: moving beyond anti-VEGF approaches. Canc Metastasis Rev 2015;34:19–40. https://doi.org/10.1007/s10555-014-9538-9.

[2] Eskander RN, Tewari KS. Incorporation of anti-angiogenesis therapy in the management of advanced ovarian carcinoma–mechanistics, review of phase III randomized clinical trials, and regulatory implications. Gynecol Oncol 2014;132:496–505. https://doi.org/10.1016/j.ygyno.2013.11.029.

[3] Graybill W, Sood AK, Monk BJ, Coleman RL. State of the science: emerging therapeutic strategies for targeting angiogenesis in ovarian cancer. Gynecol Oncol 2015;138:223–6. https://doi.org/10.1016/j.ygyno.2015.07.008.

[4] Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473–83. https://doi.org/10.1056/NEJMoa1104390.

[5] Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher EM, Brady MF, et al. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. J Clin Oncol 2019;37:2317–28. https://doi.org/10.1200/JCO.19.01009.
[6] Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484–96. https://doi.org/10.1056/NEJMoa1103799.
[7] Oza AM, Perren TJ, Swart AM, Schröder W, Pujade-Lauraine E, Havsteen H, et al. ICON7: final overall survival results in the GCIG phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer. Eur J Canc 2013;49:S4. https://doi.org/10.1016/S0959-8049(13)70070-4.
[8] Mustea A, Wimberger P, Oskay-Oezcelik G, Jungberg P, Meinerz W, Reichert D, et al. Impact of age on the safety and efficacy of bevacizumab (BEV)-containing therapy in patients (pts) with primary ovarian cancer (OC): analyses of the OTILIA German non-interventional study on behalf of the North-Eastern German Society of Gynaecological Oncology Ovarian Cancer Working Group. Ann Oncol 2016;27:vi299. https://doi.org/10.1093/annonc/mdw374.14.
[9] Della Pepa C, Tonini G, Pisano C, Di Napoli M, Cecere SC, Tambaro R, et al. Ovarian cancer standard of care: are there real alternatives? Chin J Canc 2015;34:17–27. https://doi.org/10.5732/cjc.014.10274.
[10] Pignata S, Lorusso D, Joly F, Gallo C, Colombo N, Sessa C, et al. Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: the randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17. J Clin Oncol 2018;36. https://doi.org/10.1200/jco.2018.36.15_suppl.5506. 5506–5506.
[11] Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039–45. https://doi.org/10.1200/JCO.2012.42.0505.
[12] Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer HHS Public Access Conclusions—results from final OS analysis of the phase 3 OCEA. Gynecol Oncol 2015;139:10–6. https://doi.org/10.1016/j.ygyno.2015.08.004.
[13] Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017;18. https://doi.org/10.1016/S1470-2045(16)30559-9.
[14] Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302–8. https://doi.org/10.1200/JCO.2013.51.4489.
[15] Sorio R, Roemer-Becuwe C, Hilpert F, Gibbs E, García Y, Kaern J, et al. Safety and efficacy of single-agent bevacizumab-containing therapy in elderly patients with platinum-resistant recurrent ovarian cancer: subgroup analysis of the randomised phase III AURELIA trial. Gynecol Oncol 2017. https://doi.org/10.1016/j.ygyno.2016.11.006.
[16] Rouzier R, Gouy S, Selle F, Lambaudie E, Floquet A, Fourchotte V, et al. Efficacy and safety of bevacizumab-containing neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: results from the ANTHALYA trial. Eur J Canc 2017;70:133–42. https://doi.org/10.1016/j.ejca.2016.09.036.
[17] Garcia Garcia Y. Efficacy and safety results from GEICO 1205, a randomized phase II trial of neoadjuvant chemotherapy with or without bevacizumab for advanced epithelial ovarian cancer. Int J Gynecol Canc 2019;29:1050–6. https://doi.org/10.1136/ijgc-2019-000256.
[18] Friedlander M, Hancock KC, Rischin D, Messing MJ, Stringer CA, Matthys GM, et al. A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. Gynecol Oncol 2010;119:32–7. https://doi.org/10.1016/j.ygyno.2010.05.033.
[19] Vergote I, du Bois A, Floquet A, Rau J, Kim JW, del Campo JM, et al. Overall survival results of AGO-OVAR16: a phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer. Gynecol Oncol 2019;155:186–91. https://doi.org/10.1016/j.ygyno.2019.08.024.
[20] Ledermann JA, Hackshaw A, Kaye S, Jayson G, Gabra H, McNeish I, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. J Clin Oncol 2011;29:3798–804. https://doi.org/10.1200/JCO.2010.33.5208.
[21] du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, et al. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2016;17:78–89. https://doi.org/10.1016/S1470-2045(15)00366-6.
[22] Ray-Coquard I, Cibula D, Mirza MR, Reuss A, Ricci C, Colombo N, et al. Final results from GCIG/ENGOT/AGO-OVAR 12, a randomised placebo-controlled phase III trial of nintedanib combined with chemotherapy for newly diagnosed advanced ovarian cancer. Int J Canc 2019. https://doi.org/10.1002/ijc.32606.
[23] Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014;15:799–808. https://doi.org/10.1016/S1470-2045(14)70244-X.
[24] Marth C, Vergote I, Scambia G, Oberaigner W, Clamp A, Berger R, et al. ENGOT-ov-6/TRINOVA-2: randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. Eur J Canc 2017;70:111–21. https://doi.org/10.1016/j.ejca.2016.09.004.
[25] Matulonis UA, Berlin S, Ivy P, Tyburski K, Krasner C, Zarwan C, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol 2009;27:5601–6. https://doi.org/10.1200/JCO.2009.23.2777.
[26] Ledermann JA, Embleton AC, Perren T, Jayson GC, Rustin GJS, Kaye SB, et al. Overall survival results of ICON6: a trial of chemotherapy and cediranib in relapsed ovarian cancer. J Clin Oncol 2017;35. https://doi.org/10.1200/jco.2017.35.15_suppl.5506. 5506–5506.
[27] Biagi JJ, Oza AM, ChalChal HI, Grimshaw R, Ellard SL, Lee U, et al. A phase II study of sunitinib in patients with recurrent epithelial ovarian and primary peritoneal carcinoma: an NCIC clinical trials group study. Ann Oncol 2011;22:335–40. https://doi.org/10.1093/annonc/mdq357.
[28] Pölcher M, Eckhardt M, Coch C, Wolfgarten M, Kübler K, Hartmann G, et al. Sorafenib in combination with carboplatin and paclitaxel as neoadjuvant chemotherapy in

patients with advanced ovarian cancer. Canc Chemother Pharmacol 2010;66:203–7. https://doi.org/10.1007/s00280-010-1276-2.

[29] Herzog TJ, Scambia G, Kim BG, Lhommé C, Markowska J, Ray-Coquard I, et al. A randomized phase II trial of maintenance therapy with Sorafenib in front-line ovarian carcinoma. Gynecol Oncol 2013;130:25–30. https://doi.org/10.1016/j.ygyno.2013.04.011.

[30] Kohn EC, Lee J, Annunziata CM, Minasian LM, Zujewski J, Prindiville SA, et al. A phase II study of intermittent sorafenib with bevacizumab in bevacizumab-naive epithelial ovarian cancer (EOC) patients. J Clin Oncol 2011;29. https://doi.org/10.1200/jco.2011.29.15_suppl.5019. 5019–5019.

[31] Colombo N, Mangili G, Mammoliti S, Kalling M, Tholander B, Sternas L, et al. A phase II study of aflibercept in patients with advanced epithelial ovarian cancer and symptomatic malignant ascites. Gynecol Oncol 2012;125:42–7. https://doi.org/10.1016/j.ygyno.2011.11.021.

[32] Gotlieb WH, Amant F, Advani S, Goswami C, Hirte H, Provencher D, et al. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncol 2012;13:154–62. https://doi.org/10.1016/S1470-2045(11)70338-2.

[33] Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014;15:1207–14. https://doi.org/10.1016/S1470-2045(14)70391-2.

[34] Liu JF, Barry WT, Birrer M, Lee J-M, Buckanovich RJ, Fleming GF, et al. Overall survival and updated progression-free survival outcomes in a randomized phase 2 study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. Ann Oncol Off J Eur Soc Med Oncol 2019. https://doi.org/10.1093/annonc/mdz018.

[35] Mirza MR, Åvall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol 2019;20:1409–19. https://doi.org/10.1016/S1470-2045(19)30515-7.

[36] Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 2019;381:2416–28. https://doi.org/10.1056/NEJMoa1911361.

[37] Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. Mol Canc 2019;18. https://doi.org/10.1186/s12943-019-0974-6.