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Editorial
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Anti-Angiogenetic Therapies for Ovarian Cancer: Results from Sub-Group Analysis

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Editorial

Epithelial Ovarian Cancer (EOC) is the fifth most common type of cancer in women and the fourth most common cause of cancer death in women. Current results with available therapies are far from being satisfactory and, therefore, research is focusing on researching new anticancer drugs to prolong overall survival and quality of life of patients with advanced EOC. The aim of this brief editorial is to introduce the last results of trials on anti-angiogenetic therapies for EOC and in particular to high light their outcomes in specific subgroups as well as the need of more accurate and homogeneous patients' selection for future trials design. Epithelial Ovarian Cancer (EOC) is the fifth most common type of cancer in women and the fourth most common cause of cancer death in women.As this cancer has late and nonspecific symptoms, the major part (70%–80 %) of patient presents at the time of diagnosis an advanced stage of the disease (according with The International Federation of Gynecologists and Obstetricians, FIGO III-IV). The standard of care for these patients consists of debulking surgery, followed by adjuvant intravenous Chemotherapy (CT) based on combination of carboplatin and paclitaxel. Approximately 80% of patients initially respond to CT, but more than 50% of these later relapse and only 10%-30% of such patients show long-term survival. Current results with available therapies are far from being satisfactory and therefore, research is focusing on researching new anticancer drugs to prolong overall survival and quality of life of patients with advanced EOC. In particular, there is an urgent need of new treatment options in first-line setting (primary OEC) or even more in the management of platinum-sensitive or resistant recurrence disease [1].

In the last years, several multicenter randomized large phase III trials studied new agents for the treatment of advanced EOC. In general, almost of these trials demonstrated that targeted drugs often significantly increase prolonged Progression-Free Survival (PFS), but not Overall Survival (OS); in fact, it is exceptionally difficult to show a statistically significant prolongation of OS, due to the presence of potential confounding factors such as the long post-progression survival period or the administration of multiple post-progression therapies.

It is largely known that EOC is a highly heterogeneous disease with immunohistological subtypes that differ vastly in terms of stage, chemo sensitivity, and genetic mutations. In the last years, the identification of distinct molecular pathways characteristic of individual subtypes has fueled enthusiasm for the research of targeted therapies directed to specific subgroups of patients (for example PARP inhibitor in patients with BRCA mutations).

Angiogenesis is an essential process for tumor growth and metastasis, and its pathways are undergoing intense clinical investigation for the treatment of gynecological cancers [2-4] including EOC [5]. Bevacizumab, a monoclonal humanized antibody directed against circulating Vascular-Endothelial Growth Factor (VEGF), has been the first antiangiogenic drug studied in patients with advanced EOC [6]. Two randomized phase III clinical trials (the International Collaboration on Ovarian Neoplasms trial [ICON7] [7] and the Gynecologic Oncology Group study 218 [GOG-218] [8]) demonstrated a benefit in PFS in patients with primary EOC treated with standard CT in combination with bevacizumab. For this reason, the European Medicines Agency (EMA) approved the addition of bevacizumab to standard primary treatment of EOC. Anyway, the role of this drug has been also investigated for the treatment of recurrent EOC, showing a clinically advantage as monotherapy or as combination therapy in randomized phase III trials (OCEANS trial [9] for recurrent platinum-sensitive EOC and AURELIA trial [10] for platinum-resistant EOC). These results recently led the FDA to approve bevacizumab in combinatory regimens for the treatment of

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patients with platinum-resistant recurrent EOC.

Although these four studies met their primary end-points of prolonging PFS, only two suggested an increase in OS among predefined patients' subgroups in exploratory analyses. In ICON7, the benefit of adding bevacizumab was greatest in women with high-risk progression tumor (intending FIGO stage IV or FIGO stage III and >1.0 cm of residual disease after debulking surgery). The estimated median PFS resulted 10.5 months with standard therapy compared with 15.9 months with bevacizumab in a combinatory regimen (P< 0.001). The final analysis of OS showed a significant difference among women who received the experimental treatment compared with those who received CT alone (34.5 months vs 39.3 months, P=0.003) [7]. Additionally, in GOG 218 the median OS for women with EOC at FIGO stage IV increased by 9.5 months with bevacizumab in combination with CT plus bevacizumab maintenance) [8]. These trials apparently suggest that patients with bulky disease may have a greater benefit from the targeted therapy based on bevacizumab. Although the molecular mechanisms that responsible for this better clinical response are unknown, a higher residual tumor burden, producing a relevant level of VEGF, may enable bevacizumab to exert a stronger effect on tumor microenvironment.

Currently, the optimal timing for the administration of bevacizumab in the course of the disease needs to be determined. In addition, the advantages of prolonging its administration beyond eventual tumor progression, or the benefit in re-treating patients remain to be definitively answered. It is important to remember that until now no plasmatic biomarkers have been validated to predict to response to bevacizumab, even if promising results have been obtained. For example in ICON7, the combined values of high circulating angiopoietin 1 (Ang-1) and low of tunica internal endothelial cell kinase-2 (Tie-2) concentrations were associated with significantly improved PFS for patients who received bevacizumab (23.0 vs 16.2 months, P = 0.003) [11]. Further studies on this topic are needed.

A major challenge in the success of antiangiogenic therapy directed against VEGFR is the development of tumor resistance, probably due to induction of escape mechanisms through the up regulation of other pathways, such as those of platelet-derived growth factor receptor (PDGFR) or fibroblast growth factor receptor (FGFR). Multi tyrosine kinases inhibitors (TKI), simultaneously targeting additional pathways involved in angiogenesis, may exert a higher antitumor potential, preventing also the activation of molecular pathways that normally could lead to resistance to bevacizumab. Although no TKIs have been still approved, nintedanib, pazopanib and cediranibare the most investigated agents in late trials for treating advanced EOC.

Nintedanib, an oral triple TKI of VEGFR, PDGFR and FGFR has been evaluated in a AGO-OVAR 12 phase III trial in combination with first -line CT and as maintenance therapy. The study showed a low increase, amounting of 0.6 months, in median PFS for the nintedanib group (17.2 months vs. 16.6 months, P=0.024). Most importantly, a subgroup analysis demonstrated a higher PFS increase with the use of nintedanib in not high–risk tumor or low burden tumor group, consisting in FIGO stage III and <1 cm postsurgical residual tumor deposits (27.1 vs 20.8 months, P=0.005). On the other hand, no significant difference in PFS was noted between the nintedanib and placebo arms for high-risk or high tumor burden subgroup. Serious adverse events were reported in 42% of patients in the nintedanib group and 34% of patients in the placebo group, and the most common AEs were gastrointestinal [12].

Pazopanib, an oral multi TKI of VEGFR -1, -2, -3, PDGFR, has been tested in AGO-OVAR 16 phase III trial for the treatment of patients with EOC not progressing during first-line CT. Maintenance therapy with pazopanib prolonged PFS by 4.7 months (17.9 vs 12.3 months, P=0.0021), although OS did not show any significant difference between pazopanib and placebo arms. Interestingly, most of the patients randomly assigned to the experimental arm had a low risk disease, similarly to nintedanib AGO-OVAR 12 trial. A not negligible difference between these two studies was that patients enrolled in AGO-OVAR 16 trial had already received previous CT (which may influence tumor resistance and thus the response to the drug) [13]. In general, these results seem to suggest that women with optimal surgical debulking may be suitable candidates for deeply investigating these two drugs. In the near future, more accurate patients' stratifications based on residual tumor burden should be undertaken for trying to answer this question.

Cediranib, an oral inhibitor of VEGFR-1, 2 and 3, was evaluated in ICON 6 phase III trial for the treatment of recurrent platinum-sensitive EOC in combination with CT and as maintenance therapy, showing a light improvement in median PFS (2.3 months) in patients receiving cediranib. At the best of our knowledge a subgroup analysis did not lead to significant results in the patients' subpopulation [14]. Interestingly, remarkable data were reported in a phase II open-label trial which investigated the combination of cediranib with olaparib, a PARP inhibitor. In this study, 46 women with relapsed platinum-sensitive high-grade serous or endometrioid, or BRCA-mutated EOC were randomized to receive olaparib alone (400 mg twice daily) or in combination (200mg twice daily) with cediranib (30 mg daily). Patients who received the combinatory therapy had a significant improvement in PFS compared with those treated with olaparib alone (17.7 vs 9 months, p=0.005). Interestingly, a post-hoc analysis of PFS and response rate demonstrated that the addition of cediranib improved also PFS and response rate in the BRCA wild-type or BRCA unknown population, with a median PFS of 5.7 months in the olaparib arm and 16.5 months in the combination group, and a response rate (RR) of 32% and 75%, respectively. Regarding the BRCA mutated population, the combinatory regimen led to significantly higher PFS (19.4 vs 16. 5 months) and RR (84% vs 63%) in comparison to olaparib alone [15]. Thus, this post hoc analysis demonstrated that the magnitude of improvement in PFS was surprisingly greater in the BRCA wild-type/unknown subgroup.

Currently, a number of key questions remain to be addressed for the future of multi anti-angiogenetic TKI as mono- or combinatory therapies for treating EOC. In particular, the efficacy of these drugs to treat patients who have previously received bevacizumab is unclear. Moreover, it should be also clarified better their role also in patients not receiving previous angiogenetic therapies or even as first-line therapy.

In this contest, it is necessary to under light that most of current clinical trials on advanced EOC tend to be performed without properly selecting patient for debulking surgical results or tumor characteristics, and include heterogeneous populations. The aim of surgical treatment for EOC is achieving an optimum debulking (originally defined as no residual or any tumor left of less than 1.6 cm, and recently redefined as no residual disease) [1], but an extensive surgical management is not still universally practiced and

it may arguably contribute to the variability of results in reported trials. Moreover, it is important to distinguish patients with primary EOC, with platinum-sensitive and resistant recurrent EOC as well as patients who have received previous line of CT, targeted therapy, and especially anti-angiogenetic agents.

EOC is a heterogeneous disease that now is divided by histologic subtypes and moving to even more differentiation based on molecular genetic alterations. In conclusion, clinical trial endpoints in the era of modern EOC therapeutics should to be reassessed in order to guarantee that the endpoints assessed reflect the realities of differing outcomes and meaning of those outcomes to patients afflicted. Moreover, future registration strategies will need to address cancer heterogeneity by designing trials that include smaller more homogenous patients' populations.

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