

## Commentary on Bevacizumab in Ovarian Cancer: Focus on Clinical Data and Future Perspectives

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### Ovarian Cancer

The established standard strategy for treatment of advanced Epithelial Ovarian Cancer (EOC), has been debulking surgery and platinum/taxane-based chemotherapy followed by surveillance for potential recurrence. Despite initial chemo-sensitivity to platinum/taxane doublets, most patients with advanced EOC relapse after first-line therapy and global mortality remains high.

Treatment strategies that have led to an Overall Survival (OS) improvement for newly diagnosed patients have included the addition of paclitaxel to platinum, the use of intraperitoneal cisplatin in patients with optimally cytoreduced cancer (<1 cm of residual cancer after upfront cytoreductive surgery), and incorporation of weekly paclitaxel instead of every-3-week paclitaxel as part of upfront treatment for ovarian cancer [1,2]. Neoadjuvant chemotherapy has emerged as a treatment alternative, especially in patients who are too ill or frail or whose cancer is too extensive to undergo upfront cytoreductive surgery [3]. Although trials of various biologic agents, most commonly antiangiogenics, have demonstrated Progression-Free Survival (PFS) benefit in randomized trials, no trials have demonstrated an improvement in OS [4-7].

Infact the achievement of OS improvement in ovarian cancer, a frequent standard for regulatory approval, has proven challenging despite improvements in PFS. Reasons for the difficulty in demonstrating OS improvement are not fully understood; possible reasons include the availability of many treatment options following progression, the lack of stratification of histologic subtypes in previous trial designs, thus diluting the effectiveness of agents that might have shown benefit when tested in molecularly or genomically defined subgroups, and the fact that some patients in randomized trials will eventually cross over to the other treatment, thus possibly affecting OS. In addition, trials that demonstrate a PFS benefit but no OS improvement must define a clinically and statistically meaningful PFS improvement with acceptable acute and long-term toxicities and good quality of life.

Considering new treatment strategies, at the 2010 Consensus Conference on ovarian cancer, it was agreed that angiogenesis represents one of the most promising targets in ovarian cancer [8]. Bevacizumab is the most studied antiangiogenic agent in ovarian cancer; in four consecutive randomized trials adding bevacizumab to chemotherapy in the treatment of both front-line (GOG -2018 [4], ICON-7 [5] and recurrent EOC 'platinum-resistant' (AURELIA trial [7] or 'platinum-sensitive' (OCEAN trial [6], has resulted in PFS improvement, but no OS improvement.

There are several debatable questions today about antiangiogenic therapy in ovarian cancer:

- 1) The possibility to select patients able to respond to antiangiogenic therapy
- 2) The use of bevacizumab in the neoadjuvant setting
- 3) Treatment duration in front line setting
- 4) The optimal setting for bevacizumab treatment and the use of bevacizumab beyond progression
- 5) Combination strategies

### Patients Selection

With respect to patient selection, results of exploratory subgroup analyses of both ICON7 and GOG-0218 generate intriguing hypotheses about patient selection for bevacizumab-containing therapy, and raise important questions about the definition of high risk of progression disease, based on stage and residual tumor after surgery. However, these hypotheses based on exploratory analyses require validation and it is important to note that PFS benefit is seen across almost all subgroups evaluated.

Another important issue of investigation is the search for biomarkers that may predict bevacizumab efficacy. Currently, there are no validated biomarkers for patient selection or monitoring response to anti-angiogenic therapy in any tumor type, despite multiple studies with these agents. This is due to a number of challenges, not least the complexity of angiogenesis and our limited understanding of the mechanism of action of anti-angiogenic therapies. Furthermore, validation of a predictive biomarker can only be achieved in the context of a randomised controlled trial, and in ovarian cancer, data from these studies are only now starting to emerge; exploratory analyses evaluating gene expression profiles, tumor markers and other plasma markers in the ICON7 and GOG-0218 trials have been reported [9,10], generating interesting hypotheses requiring further exploration and validation. Several of the ongoing trials also include biomarker evaluation but as yet, no robust biomarker predicting bevacizumab efficacy has been identified.

### Neoadjuvant Setting

Efficacy and safety data are beginning to emerge for bevacizumab as a component of neoadjuvant carboplatin and paclitaxel therapy in ovarian cancer. In a recent paper Petrillo et al reported that the incorporation of bevacizumab in Neoadjuvant Chemotherapy (NACT) prolongs PFS without affecting the safety of interval debulking surgery in a group of twenty-five patients with high-grade serous advanced OC treated with bevacizumab-based NACT (cases) matched with matched 50 high-grade serous advanced OC patients treated with standard NACT without bevacizumab (controls) [11]. First results of two

randomized studies were recently reported from the NOVA study, [12] and ANTHALYA trial (ClinicalTrials.gov), reporting that neoadjuvant bevacizumab regimen was feasible and tolerable.

### Treatment Duration in Front Line Setting

Both ICON-7 and GOG 218 showed that bevacizumab treatment duration is critical, and bevacizumab should be continued beyond chemotherapy to delay disease progression. Furthermore, in the group that received bevacizumab as a single agent after combination with chemotherapy, maximal separation of the PFS curves occurred at 15 months, at the end of the bevacizumab administration period. These observations are consistent with preclinical findings in a variety of tumors, including ovarian cancer models, suggesting that long-term VEGF blockade is required to achieve maximal therapeutic benefit [13].

Recently the single-arm ROSiA, assessing the safety of front-line bevacizumab-based therapy given until disease progression or for up to 36 cycles (24 months), has completed the accrual of more than 1000 patients. Safety was consistent with the established safety profile of bevacizumab. The extended duration of bevacizumab evaluated in ROSiA demonstrated median PFS of 25.5 months, the longest yet reported for front-line bevacizumab-containing therapy in ovarian cancer and comparing favorably with data from ICON7 (PFS=19.3 months) [14].

The ongoing AGO-OVAR17 randomized trial (BOOST; ClinicalTrials.gov) is designed to confirm whether bevacizumab for up to 30 months is more effective than bevacizumab given for up to only 15 months (as in GOG-0218). The trial has completed accrual.

### Optimal Setting for Bevacizumab

There are no data available to answer the important question about the optimal setting for bevacizumab combination chemotherapy, in fact all the above mentioned trials showed its activity of both front line and recurrent platinum sensitive or platinum resistant ovarian cancer.

Moreover VEGF is expressed throughout the tumor life cycle and preclinical data suggest that continuous suppression of VEGF is required to achieve and maintain tumor control [15] and the timing and mechanisms of resistance to bevacizumab are likely to be different from those for chemotherapy. In this context Bevacizumab continued beyond disease progression is an intriguing clinical hypothesis with a compelling biological rationale.

There are already evidences of improved PFS in metastatic colorectal cancer and metastatic breast cancer patients receiving bevacizumab in second-line chemotherapy after progression on first-line bevacizumab-containing therapy. Ongoing prospective phase III trials are exploring this strategy recurrent ovarian cancer (MITO-16/ MaNGO OV-2, ClinicalTrials.gov).

### Combinations

Finally other antiangiogenic agents, such as nintedanib [Vascular Endothelial Growth Factor Receptor (VEGFR) Tyrosine Kinase Inhibitor (TKI)] and trebananib (peptide-Fc fusion protein that inhibits binding of angiopoietin 1 and 2 to the Tie2 receptor), are being tested in the upfront and recurrent settings [16,17] and are currently awaiting mature results.

Among these new antiangiogenic multitarget agents the oral VEGFR TKI cediranib (43) showed promising results as reported in ICON 6 trials. In this three-arm randomized phase III trial in platinum-sensitive recurrent ovarian cancer, cediranib given in combination with platinum-based chemotherapy and then continued as a single agent resulted in significantly improved PFS and OS compared with chemotherapy alone.

The recognition that ovarian cancer is not one cancer and instead is composed of several subtypes has begun to affect treatment strategies and several compounds showed a significant activity in particular setting of ovarian cancer as PARP inhibitors as well as immunotherapy approaches. Combinations of biologics that target various pathways and exhibit preclinical synergy may represent a new treatment paradigm for advanced ovarian cancer given its genomic complexity.

Recently, provocative results from a phase II study of the combination of olaparib (PARP i) and cediranib were reported in patients with platinum-sensitive recurrent ovarian cancer [18].

Several studies combining parp inhibitors and antiangiogenic drugs as bevacizumab are ongoing as PAOLA 1 (combining bevacizumab and olaparib) or AVANOVA (combining bevacizumab and niraparib) (ClinicalTrials.gov).

The timing is right for a paradigm shift that will require optimizing surgery and enforcing appropriate evidence-based strategies in advanced ovarian cancer.

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