



## Editorial on “The AvaALL Randomized Clinical Trial”

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Angiogenesis is essential for tumor growth and blood-borne metastasis, while pharmacological inhibition of tumor-induced angiogenesis is a strategy used in several solid tumors. In advanced non-squamous non-oncogene addicted non-small cell lung cancer (NSCLC), the use of bevacizumab—a monoclonal antibody targeting vascular endothelial growth factor (VEGF)—in addition to platinum-doublet is approved for first-line treatment (1,2).

A meta-analysis of four phase II and III randomized trials on the addition of bevacizumab to a platinum base doublet showed how bevacizumab combination was able to prolong both overall survival (OS) and PFS, compared to chemotherapy alone (HR =0.9; 95% CI: 0.81–0.99, P=0.03 and HR =0.72, 95% CI: 0.66–0.79, P<0.001) (3).

This strategy includes the possibility of continuing bevacizumab after the conclusion of platinum-based chemotherapy until progression. In continuous-maintenance setting, bevacizumab has been evaluated both as single-agent and in combination with pemetrexed (4,5).

Prolonged inhibition of angiogenesis after the conclusion of platinum-based chemotherapy has an interesting biological rationale and demonstrated to be associated with an overall favorable safety profile. Preclinical models support this rationale by showing that discontinuation of anti-angiogenic treatment leads to rapid vascular regrowth followed by increased tumor growth, whereas maintenance therapy extends survival of the mice. First observations, dating back to 2006, were obtained in the RIP-Tag2 and

Lewis lung carcinoma experimental tumor models treated with the antiangiogenic multi-target kinase inhibitors AG-013736 or AG-02826 (6). More recently, Yang *et al.* found that discontinuation of anti-VEGF treatment creates a time-window of profound structural changes in the liver vasculature, which promotes metastasis (7).

Gridelli and colleagues recently published the first phase III clinical trial (AvaALL) addressing the issue of continuation of angiogenesis inhibition also beyond progressive disease, in association with second-line chemotherapy treatment (8).

This strategy has been successful in colorectal cancer and is grounded on a sound biological rationale, in relationship with potential detrimental effects of discontinuation angiogenesis inhibition (9,10).

As far as lung cancer is concerned, a retrospective analysis on advance-stage NSCLC patient treated with first line chemotherapy plus bevacizumab showed how the continuation of antiangiogenic treatment alone until progression might increase survival outcomes (11). This study sparked the interest for testing bevacizumab potential benefit beyond disease progression after first line combination treatment with standard chemotherapy in advanced non-squamous NSCLC.

In the AvaALL trial, patients with advanced non-squamous NSCLC treated with platinum-doublet plus bevacizumab in first-line setting followed by at least two cycles of bevacizumab maintenance treatment

were randomized to receive, at the time of radiological progression, either standard of care chemotherapy or standard of care plus bevacizumab. The primary end-point was overall survival (since randomization).

The primary end-point was unmet but it was underpowered according to statistical assumptions.

The slow accrual has been a problem also in the previously reported phase II trial (12). This reflects the limited diffusion of first-line treatments including an anti-angiogenic agent in the field of lung cancer. The addition of bevacizumab to first-line treatment is thus limited to non-squamous NSCLC without baseline conditions that may affect the safety profile of the treatment.

Patients with uncontrolled hypertension, hemoptysis, hemorrhagic disorders or under treatment with anticoagulant therapy are not considerable eligible for bevacizumab, as well patients with a tumor invading major blood vessels, based on a radiological assessment. This last feature has become with time far more debatable: Barlesi and colleagues demonstrated how the consistency in evaluating eligibility of patients with central tumors for bevacizumab was weak among trained radiologists (13).

The presence of brain metastases was another contraindication of antiangiogenic treatment, due to the fear of fatal cerebral hemorrhagic events. A large retrospective analysis and a prospective study, however, showed no difference of the rate of cerebral haemorrhage between patients receiving bevacizumab and patients treated only with chemotherapy (14,15).

Furthermore, additional factors can ground bevacizumab prescription in lung cancer. This is the case of presence of liver metastasis: in a non-preplanned exploratory analysis in the E4599 trial the subgroup of patients with hepatic involvement was associated with marked benefit in terms of OS (1).

Secondary end-points, progression-free survival from first to second (PFS2) and from second to third progression (PFS3), suggested the potentiality of anti-angiogenesis beyond progression. Even though not formally statistically significant, the trend for improvement in PFS following the subsequent lines of treatment suggests that prolonged inhibition of angiogenesis may have an increased impact in a clinically and/or molecularly selected population. Clinical selection based on above-mentioned toxicity-related exclusion criteria already outlines a subgroup of patients who may have better prognosis, due to the limited comorbidity and the exclusion of bulky mediastinal involvement. In addition, in the present study, patients

with ECOG performance status (PS) superior to 1 and aged 75 or older seem not to benefit from continuation of bevacizumab beyond progression. Even considering the limits of the subgroup analysis, this may underline the role of clinical selection in this setting.

Remarkably, until now no molecular predictive markers of sensitivity to antiangiogenic treatment are available in clinical practice. Many potential predictive biomarkers have been studied, including both components of the angiogenic pathway and others related to the capacity of tumor cells to respond to metabolic changes induced by inhibition of angiogenesis (16-20).

On this basis, we believe that future studies on the topic should include biomarkers' based preplanned analyses.

Even though, as the authors acknowledge, their findings have no direct applications in clinical practice, due to the statistical limitations and, above all, to the changing clinical standard, the concept of continuation of anti-angiogenesis beyond progression might be considered in emerging clinical settings for bevacizumab.

The first one concerns treatment of EGFR-mutated advanced NSCLC. Angiogenesis is essential for tumor growth and EGFR-related signaling axis plays an important role in its regulation. In particular, mutant EGFR seems to be able to up-regulate VEGF production, suggesting a potential synergy between antiangiogenic agents and EGFR-tyrosine kinase inhibitors (TKIs) (21). Randomized trials evaluated the association of bevacizumab with erlotinib as first line treatment and confirmed an improvement in PFS, even though an increase in OS has not been demonstrated (22,23).

The second potential field of application of bevacizumab beyond progression in lung cancer is treatment of a clinically selected population of non-oncogene addicted advanced NSCLC treated with carboplatin-paclitaxel in combination with bevacizumab and atezolizumab in first-line setting (24). Evidence accumulated about the immunosuppressive role of VEGF, including dysfunctional lymphocyte trafficking into the tumor, hampered dendritic cells maturation, higher tumoral expression of PD-L1 and recruitment of immunosuppressive immune cell subsets, such as T-regulatory cells and myeloid-derived suppressor cells (25). Interestingly the subset of patients with liver metastases seems to benefit more from this combination, thus confirming the potential existence of clinically defined subgroups of patients who may have particular benefit from antiangiogenic treatment. In conclusion, this manuscript suggests that the strategy of continuing bevacizumab

beyond progression deserves further investigation in upcoming clinical applications of antiangiogenic treatment.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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