

Bevacizumab in small cell lung cancer

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Comment on: Tiseo M, Boni L, Ambrosio F, *et al.* Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial. *J Clin Oncol* 2017;35:1281-7.

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The randomized phase III, open-label, multicenter clinical trial, based on 205 patients with extensive-disease (ED) of small-cell lung cancer (SCLC), evaluated the efficacy and the safety of humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), in combination with etoposide and cisplatin in first line chemotherapeutic treatment (1). This study was supported by the “Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC)—Agenzia Italiana del Farmaco FARM6PMFJM”. A random assignment was made for the patients to either receive cisplatin and etoposide with or without bevacizumab. The evaluation of the overall survival (OS) was the primary end point. In the bevacizumab arm, at a median follow-up of 34.9 months, there was an improvement in the median OS (9.8 *vs.* 8.9 months; HR =0.78) showing, respectively, a 1-year survival rates of 37% and 25% (HR =0.78; 95% CI, 0.58–1.06; P=0.113). Moreover, patients reporting an objective response were in proportion 58.4% and 55.3% for the bevacizumab and the control arms, respectively. Ninety six patients were treated with chemotherapy and bevacizumab and 41 of them (42%) continued with the monoclonal antibody beyond the pre-planned six cycles of treatment with maintenance, in median, of four more cycles. The disease progression caused the interruption of bevacizumab in 65.8% of patients. The bevacizumab-based maintenance had a statistically significant effect over the OS (HR =0.60; P=0.011) with, as expected, a well-tolerability; the only frequent adverse registered event in

the bevacizumab arm was the hypertension (grade 3 or 4; 6.3% *vs.* 1.0%; P=0.057).

In several different tumours, such as non-small cell lung cancer (NSCLC) (2-5), the effect of the anti-angiogenic antibody on the survival was reported. In NSCLC, bevacizumab is now approved in combination with the standard platinum based chemotherapy or as maintenance after chemotherapy, for the treatment of NSCLC patients without driver-mutations (3-5). On the counterpart, in SCLC, the randomized trials using bevacizumab added to standard chemotherapy showed poor results (6).

In 2011, a randomized phase II trial based on chemotherapy with bevacizumab versus chemotherapy plus placebo in previously untreated extensive-stage disease-SCLC (SALUTE) (7) has been performed. The progression-free survival (PFS), indicated as the primary end-point, was met; however, the advantage of 5.5 months in the bevacizumab-based arm versus the 4.4 months in the placebo-based arm was not correlated with an increased OS, which remained longer in the control arm (9.4 *vs.* 10.9 months). The IFCT-0802 study confirmed this trend, failing to show that bevacizumab-based treatment was able to improve the survival (8).

The SCLC is considered a highly proliferating disease with higher tumor response rates; thus, the maintenance approach aiming to prolong the initial response to the standard chemotherapy is strongly supported due to its high tumor spreading nature. Targeted therapies, such

as bevacizumab, with a good toxicity profiling could be administered for longer periods and are considered an ideal approach for the maintenance treatment. However, the use of new targeted therapies as maintenance compared to placebo control did not showed any advantage in term of survival as dispatched in the recent meta-analysis on SCLC (9). In contrast, Tiseo *et al.* showed patients receiving maintenance-based bevacizumab had a significantly improved OS (1). Considering the possible bias related to only patients who did not progress after chemotherapy accessed to maintenance-based bevacizumab, in our opinion, future randomized trials with specified end-points should investigate the issue of bevacizumab-based maintenance approach in the management of patients with SCLC who respond to first line therapy.

It is also noteworthy, there is a lack of validated predictive factors that could foresee a response to bevacizumab (8,10-12); notwithstanding this fact, there are few clinical reports suggesting that hypertension has a potential role in defining responders versus no-responders to the VEGF-targeting monoclonal antibody (13). A pre-planned subgroup analysis reported by Tiseo *et al.* (1) indicated that sex, in favour to females, is a potential interactor with bevacizumab, but without providing exhaustive indications or explanations. Therefore, the issue of clinical or biological markers predictive of response to bevacizumab in SCLC is unresolved and future prospective trials on this topic are awaited. In the era of immunotherapy, it should be noted SCLC has a high immunogenic biological profile, partially due to the loads of mutations, supporting the newly encouraging results using specific immunotherapeutic approaches, like checkpoint inhibitors, capable of arousing the immune system against this cancer (14). In this scenario, it would be interesting to further investigate how immunotherapy in combination with bevacizumab-based maintenance and chemotherapeutic regimen would improve the OS in SCLC. There is, therefore, a strong rationale to support a multi-directional therapeutic intervention as a valid alternative approach for the SCLC management.

To conclude, in SCLC, the addition of bevacizumab to standard first-line platinum-etoposide based chemotherapy did not show an increase on patients' survival. Considering the report by Tiseo *et al.*, there is a clinical need to test new biological drug based maintenance approach in SCLC. Furthermore, in our viewpoint, new clinical trials on maintenance therapy in SCLC should also clearly consider potential surrogate biomarkers predictive of response/resistance in order to achieve a better selection of candidates

who will have benefit to the therapy based on single or multi-directional biological drug-based maintenance treatment.

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Footnote

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

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