Letter to the Editor

Is there still room for anti-angiogenic agents in small cell lung cancer?

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Hamilton G, Rath B. Targeting angiogenesis in small cell lung cancer. Transl Cancer Res 2017;6:S522-S8.

Kallam A, Ganti AK. Bevacizumab in extensive-disease small cell lung cancer: the search continues. Transl Cancer Res 2017;6:S537-8.

Song SY, Park CK, Oh IJ, *et al.* Angiogenesis inhibitors for small cell lung cancer. Transl Cancer Res 2017;6:S539-40.

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We thank the authors of the editorials (1-4) in *Transl Cancer Res* for their comments on the GOIRC-AIFA FARM6PMFJM trial (5). This is the first randomized prospective phase III study assessing the role of adding bevacizumab to standard platinum-etoposide chemotherapy on survival outcome in the first-line treatment of extensive stage (ES) small cell lung cancer (SCLC).

This trial was designed considering the strong rational of angiogenesis inhibition also in SCLC as in other tumor types, as underlined by Hamilton and Rath (3), and some previous positive results in single arm phase II studies evaluating bevacizumab in ES-SCLC patients, as showed by Kallam and Ganti (2).

Starting from these results, our study, the largest randomized study to date using vascular endothelial growth factor (VEGF)-targeted therapy in SCLC, was planned and 40 Italian oncology centers were involved. The trial was designed with an ambitious statistical assumption: an improvement in the 1-year survival rate from 40% to 58%, corresponding to an equivalent median survival improvement from 9 to 15 months [a hazard ratio (HR) of 0.60]. This optimistic goal was chosen taking into account the feasibility in term of accrual of a non-profit study and considering that local authority [Agenzia Italiana del Farmaco (AIFA)] would have evaluated, for practice changing in SCLC, only a clinically significant survival improvement, given the adjunctive toxicity and cost of bevacizumab.

A total of 204 patients were randomized to receive a combination of either cisplatin or carboplatin and etoposide for a maximum of six cycles or the same regimen with bevacizumab (7.5 mg/kg) that was continued as maintenance until progression. The results of our trial showed a non-significant improvement in overall survival (OS), the primary end-point, with a median of 8.9 months in the chemotherapy-only group compared with 9.8 months in the bevacizumab group (HR: 0.78; 95% CI: 0.58–1.06; P=0.113). Median PFS was 5.7 *vs.* 6.7 months, favoring bevacizumab treatment (HR: 0.7; 95% CI: 0.54–0.97; P=0.030). The signal of improved PFS and trend toward OS benefit is consistent with results from prior randomized clinical trials using anti-angiogenic agents in this disease (6). In particular, these data are similar at those obtained in the SALUTE phase II trial, as underlined also by Song *et al.* (1); this study, that randomized 102 patients, met its primary end point of improvement in PFS (from 4.4 to 5.5 months; HR: 0.53; 95% CI: 0.32–0.86), but no improvement in OS was observed (6).

To explain the PFS benefit with the absence of survival advantage in our study, the data of second-line therapy is unfortunately not available and its potential influence on the final OS results is unknown. We know that the profilactic cranial irradiation (PCI) (which it was at the investigator's choice) was correlated with a survival benefit even after adjustment to treatment arm and that there was a not negligible imbalance between the two arms: PCI was received by 33.3% patients in the control arm and only in 19.5 % in the experimental arm. This could have worsened the performance of the bevacizumab arm.

However, it is necessary underline that the planned survival improvement in the GOIRC-AIFA FARM6PMFJM trial was optimistic. It was probably too large, but reasonable considering costs, sustainability and feasibility. The relative small sample size does not allow showing a possible smaller survival gain. In this context, the absence of predictive factors of anti-angiogenic agents makes everything more difficult, as

reported also in the editorials (1-4). Considering the reported OS HR of 0.78, the doubt remains whether a larger trial with the more modest yet still clinically meaningful end-point (i.e., of a 3-month improvement in OS) might have been positive. This consideration is relevant also keeping in mind the survival benefit obtained with bevacizumab combined with carboplatin-paclitaxel in advanced NSCLC (from 10.3 to 12.3 months, with an HR of 0.79) (7).

Moreover, is interesting to speculate, considering the statistically significant OS effect with bevacizumab in patients who received maintenance treatment according a landmark analysis, whether continuing bevacizumab after progression into later lines of therapy for eligible patients could have yielded additional benefit. Our results confirm those of the Alliance trial (8), which demonstrated better PFS with sunitinib maintenance compared with placebo and strengthen the hypothesis that the maintenance strategies with anti-angiogenic agents may have better efficacy than an up-front treatment in SCLC patients, as remarked by Roviello and Generali (4).

Actually, there is an urgent need for new drugs and strategies of SCLC treatment. Preliminary data of trials with immune-checkpoint inhibitors are promising results (9). The pivotal role of VEGF in modulating the tumor microenvironment and the cross-talk between angiogenesis and tumor immunity (10) strongly support the combinations of anti-angiogenic agents and immune-checkpoint inhibitors. In the next future it would be interesting to investigate the combination of chemotherapy, anti-angiogenic agents and immunotherapy as first-line with a maintenance part in the therapy of ES-SCLC.

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References

1. Song SY, Park CK, Oh IJ, et al. Angiogenesis inhibitors for small cell lung cancer. Transl Cancer Res 2017;6:S539-40.
2. Kallam A, Ganti AK. Bevacizumab in extensive-disease small cell lung cancer: the search continues. Transl Cancer Res 2017;6:S537-8.
3. Hamilton G, Rath B. Targeting angiogenesis in small cell lung cancer. Transl Cancer Res 2017;6:S522-8.
4. Roviello G, Generali D. Bevacizumab in small cell lung cancer. Transl Cancer Res 2017;6:S421-3.
5. 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.
6. Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small cell lung cancer: Results from the SALUTE trial. J Clin Oncol 2011;29:2215-22.
7. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.
8. Ready NE, Pang HH, Gu L, et al. Chemotherapy With or Without Maintenance Sunitinib for Untreated Extensive-Stage Small-Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase II Study-CALGB 30504 (Alliance). J Clin Oncol 2015;33:1660-5.
9. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and Nivolumab plus Ipilimumab in recurrent small cell lung cancer (CheckMate 032) a multicentre open label phase1/2 trial. Lancet Oncol 2016;17:883-95.
10. Manegold C, Dingemans AC, Gray JE, et al. The Potential of Combined Immunotherapy and Antiangiogenesis for the Synergistic Treatment of Advanced NSCLC. J Thorac Oncol 2017;12:194-207.

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