Letter to the Editor

Is the door open to further investigation with antiangiogenesis in SCLC?

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We thank Dr. Goto for his Editorial (1) on GOIRC-AIFA FARM6PMFJM study, the first randomized phase III trial evaluating the survival impact of bevacizumab combined to standard cisplatin-etoposide respect cisplatin-etoposide alone as first-line therapy of extended disease small cell lung cancer (SCLC) (2).

Our Italian multicenter trial shows that the addiction of bevacizumab to platinum-etoposide is practicable, well tolerated and able to lead a small statistically significant benefit in progression-free survival (PFS), but not in overall survival (OS), the primary end-point, respect to standard chemotherapy alone.

Two hundred and four patients were randomized to receive a combination of either cisplatin or carboplatin and etoposide for a maximum of 6 cycles or the same regimen with bevacizumab (7.5 mg/kg). Patients randomized to experimental arm continued bevacizumab alone as maintenance therapy until disease progression or for a maximum of 18 courses. The results showed a non-significant improvement in OS, with a median of 8.9 months in the chemotherapy arm compared with 9.8 months in the bevacizumab arm (HR: 0.78; 95% CI, 0.58 to 1.06; P=0.113); median PFS was 5.7 *vs.* 6.7 months, in favor to bevacizumab treatment (HR: 0.7; 95% CI, 0.54 to 0.97; P=0.030).

The survival results obtained in this trial are consistent with those of prior studies performed using anti-angiogenic agents in SCLC (3,4). For example, these data are similar to those obtained in the SALUTE phase II trial, that randomized 102 patients to the same regimens; this study met its primary end-point of improvement in PFS (from 4.4 to 5.5 months; HR: 0.53; 95% CI, 0.32 to 0.86), but similarly no statistically significant benefit in OS was observed (3).

As underlined by Dr. Goto (1) and also in editorial of Neal and Wakelee in the Journal of Clinical Oncology (5), the planned survival improvement was ambitious (1-year survival rate from 40% to 58%, corresponding to a median OS from 9 to 15 months) and the relative small sample size does not allow to demonstrate a possible smaller survival benefit. This optimistic goal was chosen, when planning this study, taking into account the feasibility in term of accrual of a non-profit study in this disease and that the government funding body (AIFA) would have considered for practice-changing in SCLC only a clinically significant survival improvement, given the toxicity and cost of bevacizumab.

When primary objective of this trial was planned, had the bar been raised too high? Higher than established by ASCO Perspective for example in squamous cell lung cancer (improvement in OS of 2.5–3 months with a HR of 0.77–0.80) (6), but the only reasonable considering costs, sustainability and feasibility of a non-profit trial in our country and, anyway, plausible accounting the results achieved with bevacizumab in other tumor types (7). In this context, the absence of predictive factors of anti-angiogenic agents is also a significant limiting factor.

Considering the reported OS HR of 0.78, the doubt remains as to whether a larger trial with a more modest, but clinically relevant, end-point (i.e., of a 3-month improvement) might have been met. This consideration, as also cited by Goto, 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) (8). Moreover, it is interesting to speculate, considering the statistically significant OS benefit in patients who received bevacizumab maintenance according a landmark analysis, whether using bevacizumab also after progression combined with later therapy lines could have yielded additional benefit.

Also Goto underlines these findings and, therefore, *another disappointing result*, *but how good is it?* This trial is negative, but the PFS improvement observed, as in others performed with similar drugs, justify, in our opinion, further studies with new anti-angiogenic drugs in SCLC, in particular in the maintenance strategy. The possibility to maintain open the door to further investigation with anti-angiogenesis in SCLC is also related to recent results with immunotherapy in pre-treated SCLC patients (9) and the strong rational to combined anti-angiogenic agents and immunotherapy (10). In fact, a trial of combined immunotherapy, chemotherapy and anti-angiogenic treatment as first-line strategy is under consideration within the GOIRC cooperative group for advanced SCLC.

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Footnote

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

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