



Angiogenesis inhibitors for 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 FARM6PMEJM Trial. *J Clin Oncol* 2017;35:1281-7.

Submitted Mar 31, 2017. Accepted for publication Apr 12, 2017.

doi: 10.21037/tcr.2017.04.22

View this article at: <http://dx.doi.org/10.21037/tcr.2017.04.22>

Small-cell lung cancer (SCLC) accounts for approximately 12–15% of all lung cancers and is characterized by a rapid growth rate and metastasis at the time of diagnosis. Despite its initial sensitivity to first-line chemotherapy, rapid acquisition of resistance to subsequent lines of therapy is usually observed. Although there is a plethora of new drugs being developed for non-small cell lung cancer (NSCLC), there is still a shortage of treatment regimens other than the combination therapy containing platinum and etoposide or irinotecan.

SCLC is known to over-express vascular endothelial growth factor (VEGF) (1). Consequently, bevacizumab, an angiogenesis inhibitor, is expected to have an inhibitory effect on SCLC. The use of bevacizumab along with first line carboplatin and paclitaxel demonstrated a median overall survival (OS) improvement of 2 months in the phase III Eastern Cooperative Oncology Group (ECOG) 4599 trial, and thus, was approved for NSCLC treatment (2).

There have been several phase II trials using bevacizumab for the treatment of SCLC (3-6). Among them, the Study of Bevacizumab in Previously Untreated Extensive Stage Small Cell Lung Cancer (SALUTE) trial (6) used a randomized design, in which 102 patients were administered a combination of cisplatin/carboplatin and etoposide, with or without bevacizumab. The addition of bevacizumab significantly improved progression-free survival (PFS) from 4.4 to 5.5 months [hazard ratio (HR), 0.53; 95% confidence interval (CI), 0.32 to 0.86]. However, no improvement in OS was observed.

Similar to the SALUTE trial, Tiseo *et al.* (7) recently published a phase III randomized study using bevacizumab in combination with platinum and etoposide. In this trial, 204 patients received platinum and etoposide, with or without additional bevacizumab (7.5 mg/kg intravenously

every 3 weeks, for up to 1 year). The study failed to meet the primary endpoint of OS improvement and displayed a median OS of 8.9 months in the chemotherapy-only group, and 9.8 months in the chemotherapy plus bevacizumab group (HR, 0.78; 95% CI, 0.58 to 1.06; $P=0.113$). However, median PFS showed significant improvement with the addition of bevacizumab (5.7 versus 6.7 months, HR, 0.7; 95% CI, 0.54 to 0.97; $P=0.030$). There was no difference in response rates or toxicities between the two arms.

Tiseo *et al.* (7) hypothesized that an improvement of 6 months (from 9 to 15 months, with a HR of 0.6) could be achieved in OS, which would require a sample size of 206. However, considering previous published evidence, the expectation of a 6-month OS benefit appears to be too optimistic. In the ECOG 4599 trial (2), a difference of just 2 months (12.3 versus 10.3) was observed with a sample size of 878 patients. Since the observed HR in this trial was 0.78, it might have been successful if they set the OS difference at 2 months. However, a larger sample size is required to prove such a modest difference in OS. Therefore, achieving significant OS benefit is difficult for SCLC patients, since they comprise a relatively small proportion of lung cancer patients.

The AVAiL trial, which followed the ECOG 4599 trial, did not show an OS improvement with the addition of bevacizumab, although an improvement in response and PFS were observed (8). Among various confounding factors, one must consider that OS can be influenced by the subsequent line of treatment used after progression is noted, following the end of first line clinical trial. However, the Tiseo *et al.* (7) did not include the data about second line treatment after progression.

Nevertheless, Tiseo *et al.* (7) observed a statistically

significant effect of bevacizumab on OS in patients who received it as maintenance therapy (HR, 0.60; 95% CI, 0.40 to 0.91; $P=0.011$). Since their OS and PFS Kaplan-Meier curves showed a separation between the groups after 6 months, it is possible that maintenance bevacizumab resulted in an additional benefit.

In view of the unmet need of successful treatment for SCLC, despite continued efforts in the past decades, there is an urgent need for better treatment regimens. With the success of immunotherapy in the treatment of SCLC (9), trials combining immunotherapy, angiogenesis inhibitors, and chemotherapy may be designed in the future.

In conclusion, Tiseo *et al.* (7) reported PFS improvement in SCLC patients by using bevacizumab in the largest randomized trial to date and showed likelihood of eventual OS benefit.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Shaohua Cui (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.04.22>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Song SY, Park CK, Oh IJ, Kim YC. Angiogenesis inhibitors for small cell lung cancer. *Transl Cancer Res* 2017;6(Suppl 3):S539-S540. doi: 10.21037/tcr.2017.04.22