Editorial Commentary

Tarlatamab: a potential new option for recurrent small cell lung cancer

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Small cell lung cancer (SCLC) is a highly aggressive malignancy with limited therapeutic options, particularly after the frontline setting.

The National Comprehensive Cancer Network (NCCN) guidelines on SCLC recommend that if, the relapse occurs within, 6 months, the options are either oral or intravenous (IV) topotecan, lurbinectedin, or a clinical trial (1). Other recommended regimens are taxanes, irinotecan, temozolomide in the presence of brain disease especially, and CAV (cyclophosphamide, doxorubicin, vincristine) chemotherapy. Bendamustine is category 2B because it showed some activity in a clinical trial (2). In patients who have relapsed for more than 6 months after initial therapy, the recommendation is to give the original regimen (3). Lurbinectedin is the only drug that has been approved recently, and this was in June 2020 (4). It is standard practice to rechallenge for relapse after 6 months from treatment based on a French study. In this study patients with SCLC who have progressed at least 90 days after completion of first-line treatment were randomly assigned to topotecan or platinum rechallenge (5). Interestingly, the median progression-free survival (PFS) was better in patients who were rechallenged with platinum at 4.7 *vs.* 2.7 months in patients treated with topotecan (HR, 0.57; 90% CI: 0.41–0.73; P=0.0041) There was a larger overall response rate (ORR) difference. It was 49% for platinum therapy *vs.* 25% for topotecan (P=0.0024). Not clear benefit in OS. However, recent advances in novel therapeutic approaches have shown promising results in treating this challenging disease.

The notch signaling pathway is a regulator of neuroendocrine differentiation in SCLC (6). The inhibitory notch ligand delta-like ligand 3 (DLL3) is aberrantly expressed on the surface of up to 85% of SCLC cells and minimally expressed in normal tissues, making it a compelling therapeutic target (7). The DLL3-targeted antibody-drug conjugate rovalpituzumab tesirine showed clinical antitumor activity in patients with SCLC (8).

One of the first drugs specifically developed to target DLLE was rovalpituzumab-Tesirine, an antibody-drug conjugate containing a DLL3-targeting antibody tethered to a cytotoxic agent pyrrolobenzodiazepine by means of a protease-cleavable linker. Despite initial encouraging data, Rova-T failed to showed superiority to topotecan in the 2nd line (9). The disappointing result was more likely consistent with general effects of the pyrrolobenzodiazepine payload rather than the DLL3 target.

Unlike Rova-T, Tarlatamab, a first-in-class DLL3-targeted bispecific T cell engager. DLL3 is a cell surface protein that is overexpressed in the majority of SCLC tumors but is not expressed in normal adult tissues, making it an attractive therapeutic target.

Tarlatamab binds to both DLL3 on cancer cells and CD3 on the surface of T cells, bringing them in close proximity

and triggering T cell-mediated killing of cancer cells. This targeted approach may spare healthy cells treatment-related toxicity.

A recent open-label, phase 1 study evaluated the safety and efficacy of tarlatamab in patients with recurrent SCLC who had previously received at least one line of therapy (10). The study enrolled 107 patients. Patients had received a median of two prior lines of therapy, with roughly 50% exposed to programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors. The response rate was 23.4% (95% CI: 15.7–32.5%) and two patients exhibited radiologic complete responses. The median duration of response was 12.3 months (95% CI: 6.6–14.9) and progression-free survival was 3.7 months (95% CI: 2.1–5.4). The median overall survival was 13.2 months (95% CI: 10.5 to not reached). DLL3 expression appeared to be correlated to clinical benefit. Finally, the toxicity profile showed grade 3 or higher adverse events in 30.8% of participants. All cytokine release syndrome (CRS)-related toxicities were reversible, and none resulted in discontinuation of tarlatamab although 12 patients (11.2%) experienced grade ≥3 neurologic AEs.

While this study is still in early stages, the results are encouraging. Patients who have recurrent SCLC face a bleak prognosis, with limited treatment options and a median overall survival of less than a year. Tarlatamab offers a potential new approach to treating this aggressive cancer, and its early success has sparked interest in further research. Though the data are encouraging we have to bear in mind that the population in this study does not reflect the real world. Patients were, as expected, heavily selected, being rather fit despite being exposed to several lines before and rather younger, median age 63 and no brain metastases. Despite treating a rather fit and younger cohort compare to real world one, the grade III toxicity was up to 45% and the discontinuation rate reached 86%. We believe that, to succeed in later phase, a correct patient selection, possibly biomarker driven, will be explored. Further challenge might be represented by the need to administer the drug, given the risk of CRS, while in-patient, increasing financial burden on the health system.

Of course, there are still many questions that need to be answered. The study was small, and larger trials will be needed to confirm the drug's safety and efficacy. There is also the question of whether tarlatamab can be combined with other treatments to enhance its efficacy. As stated, 50% of patients had not received immunotherapy in the phase I trial mentioned above. Immunotherapy provides long term benefits for a small subset of patients with SCLC (11). This could represent a potential combination, though cytokine release syndrome may be a limiting factor. The role of tarlatamab in patients with comorbidities or with poor performance status, a known negative prognostic factor, is also uncertain (12).

A better understanding of the pathologic and molecular characteristics of SCLC remain essential to the identification of biomarkers that will aid in drug development and/or better match patients' tumor subtypes with available treatment options. Without a clear improvement in patients' selection, we doubt that the strategy "one size fts them all" would go too far in SCLC.

However, the early results are promising, and tarlatamab represents a significant step forward in the treatment of recurrent SCLC. At the very least, it will represent an additional therapeutic option in a field with limited lines of treatment. As experts in the field, it is important for us to stay informed about this new therapy and to continue to follow its progress. We must also advocate for further research and development of innovative treatments like tarlatamab, as we work to improve outcomes for patients with hard-to-treat cancers such as SCLC.

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