NEW FIRST-LINE TREATMENT FOR SMALL-CELL LUNG CANCER

TRIAL SUMMARY: The addition of atezolizumab improves survival

Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *NEJM*. 2018 Sep 25. doi: 10.1056/NEJMoa1809064. [Epub ahead of print] Presented at WCLC, September 2018, Toronto.

Enhancing tumour-specific T-cell immunity by inhibiting programmed death ligand 1 (PD-L1)–programmed death 1 (PD-1) signaling has shown promise in the treatment of extensive-stage small-cell lung cancer (SCLC). Combining checkpoint inhibition with cytotoxic chemotherapy may have a synergistic effect and improve efficacy. This double-blind, placebo-controlled, phase 3 trial evaluated atezolizumab plus carboplatin and etoposide in treatment-naive patients with extensive-stage SCLC. A total of 403 patients were randomly assigned to receive carboplatin and etoposide with either atezolizumab or placebo for four 21-day cycles (induction phase), followed by a maintenance phase during which they received either atezolizumab or placebo (according to the previous random assignment). Treatment was continued until the appearance of unacceptable toxic effects, disease progression, or lack of additional clinical benefit. The two primary endpoints were progression-free survival (PFS) and overall survival (OS) in the intention-to-treat population.

Results: At a median followup of 13.9 months, the median OS was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio [HR] for death, 0.70; 95% confidence interval [CI]: 0.54–0.91; p=0.007). Median PFS was 5.2 months and 4.3 months, respectively (HR for disease progression or death, 0.77; 95% CI: 0.62–0.96; p=0.02). The safety profile of atezolizumab plus carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents, with no new findings observed. The addition of atezolizumab to chemotherapy in the first-line treatment of extensive-stage SCLC resulted in significantly longer OS and PFS than chemotherapy alone.

COMMENTARY: Extensive-stage SCLC has a rapid clinical course and is associated with high mortality, with a median OS of 10 or 11 months.[1,2] Combination platinum chemotherapy has been the standard of care for decades and has yet to be surpassed by other combinations or agents in the first-line setting.

Immune checkpoint inhibitors have shown some efficacy in the pretreated SCLC population.[3] Accelerated US Food and Drug Administration (FDA) approval of nivolumab was granted in August 2018 for the treatment of patients with extensive SCLC whose cancer has progressed after platinum-based chemotherapy and at least one other line of therapy. Approval was based on CHECKMATE 032 trial findings that, while only 12% of patients had a response, those who responded had a median duration of response of 17.9 months. Expression of tumour PD-L1 in SCLC is relatively low[4] and tumour PD-L1 status did not influence response overall in this trial cohort.

The IMpower133 study compared the combination of a PD-L1 inhibitor, atezolizumab, with standard-of-care carboplatin/etoposide vs a placebo-controlled cohort treated with combination chemotherapy alone.[5] The atezolizumab/placebo was continued in a maintenance fashion after the completion of 4 cycles of platinum-based therapy.

The presentation at the 2018 World Conference on Lung Cancer reported the first analysis after a median of 13.9 months followup. The addition of atezolizumab resulted in a median OS benefit of 2 months (HR 0.70) and did not compromise the delivery of standard chemotherapy. The experimental and control group survival curves overlapped for the first 6 months and only started to separate at approximately 7 months.

Dr. Natasha Leighl, the discussant, questioned whether the OS benefit was due to the synergistic effects of chemotherapy and immunotherapy and/or the maintenance use of atezolizumab. The median number of cycles of atezolizumab delivered was 7, including the chemotherapy induction phase. The relatively short average duration of checkpoint inhibition in comparison with other tumour types may help support

IN BRIEF

Already known

- Extensive-stage small-cell lung cancer (SCLC) is an aggressive thoracic malignancy with a median overall survival (OS) of less than 1 year. Platinum combination chemotherapy has been the standard-of-care first-line treatment for extensive-stage SCLC for over 2 decades.

What this study showed

- The addition of atezolizumab to platinum combination chemotherapy increases the median OS by 2 months with an acceptable toxicity profile. Administration of chemotherapy was not disrupted by the addition of immunotherapy.

Next steps

- Pending regulatory approval, atezolizumab with platinum combination chemotherapy is a new standard of care for good performance-status patients with chemotherapy-naive extensive-stage SCLC.

adoption of this therapy by health policy makers for treatment of this very aggressive disease.

Subgroup analysis of baseline characteristics, including sex, age, Eastern Cooperative Oncology Group (ECOG) status and liver metastases all favoured the atezolizumab arm. The presence of brain metastases at baseline favoured chemotherapy, however this may reflect the overall poor prognosis associated with this condition. Blood tumour mutational burden (TMB) was tested as a predictive biomarker for OS at 2 different thresholds, ≥10 and 16 mutations/megabase. No correlation was seen, suggesting that the use of blood-borne assessments of TMB may be less relevant in SCLC than in NSCLC.[6]

As highlighted by Dr. Leighl, the trial selected for patients of good performance status, so results may be difficult to replicate in the real world. It was suggested that more in-depth biomarker analysis, longer followup and future trials will help identify patient subsets that stand to benefit most from the addition of atezolizumab. While the improvement in OS is modest, it is the first trial to demonstrate a significant benefit for SCLC and hopefully represents a first step in greater progress for this disease.

References

1. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol*. 1992 Feb;10(2):282–91.
2. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol*. 2002 Dec 15; 20(24):4665–72.
3. 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, phase 1/2 trial. *Lancet Oncol*. 2016;17:883–95.
4. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). *J Thorac Oncol*. 2018; 13:1393–9.
5. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *NEJM*. 2018 Sep 25. doi: 10.1056/NEJMoa1809064.
6. Gandara DR, Paul SM, Kowanetz,M et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. *Nat Med*. 2018;24:1441–8.