Editorial

KEYNOTE-028: how do we use immunotherapy in small cell lung cancer?

Jose M. Pacheco, D. Ross Camidge

Thoracic Oncology Program, University of Colorado Cancer Center, Aurora, Colorado, USA

Correspondence to: D. Ross Camidge, MD, PhD. Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Mailstop F704, Room ACP 5236, Aurora, CO 80045, USA. Email: ross.camidge@ucdenver.edu.

Provenance: This is an invited Editorial commissioned by Guest Section Editor Dr. Minghui Zhang, MD, PhD (Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China) and Editor-in-Chief Prof. Rafael Rosell, MD, PhD (Director, Cancer Biology & Precision Medicine Program Catalan Institute of Oncology, Germans Trias i Pujol Health Sciences Institute and Hospital Badalona, Barcelona, Spain).

Comment on: Ott PA, Elez E, Hiret S, *et al*. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the Phase Ib KEYNOTE-028 study. J Clin Oncol 2017;35:3823-9.

Submitted Sep 20, 2017. Accepted for publication Sep 28, 2017.

doi: 10.21037/tlcr.2017.10.02

View this article at: http://dx.doi.org/10.21037/tlcr.2017.10.02

Recently, PD-1 axis inhibition has started to show activity in small cell lung cancer (SCLC), enough to suggest that, at last, a new treatment option for SCLC may have arrived. Nivolumab and nivolumab + ipilimumab are now both listed in the NCCN guidelines for second line or beyond therapy in SCLC, based on data from the Checkmate-032 study, although neither of these regimens has yet been approved by the FDA (1). Additionally, a small phase Ib study (KEYNOTE-028) recently published in *The Journal of Clinical Oncology* by Ott *et al.* has explored the use of pembrolizumab monotherapy in previously treated extensive stage SCLC (2). The emergence of immunotherapy as a therapeutic option in SCLC is exciting, but there is still a lot to learn about its true potential in this disease.

In KEYNOTE-028, the overall response rate (ORR) was 33% with pembrolizumab monotherapy. However, there were only 24 patients on this study and all patients were preselected for tumors demonstrating PD-L1 staining ≥1%. The median PFS was 1.9 months and the median OS was 9.7 months. Both platinum sensitive and resistant patients were enrolled on this study, although the relative benefit in these two subgroups was not assessed (2).

While the ORR to pembrolizumab in KEYNOTE-028 is encouraging, a larger trial with nivolumab, another PD-1 inhibitor, showed more modest monotherapy activity. Specifically, the ORR to nivolumab monotherapy in Checkmate-032 was 10% (n=98). In Checkmate-032, different dosing combinations of nivolumab and the CTLA-4 antagonist, ipilimumab, were also explored, initially sequentially and then later in a randomized fashion. The ORR was 23% for nivolumab 1 mg/kg + ipilimumab 3 mg/kg q 3 weeks ×4 doses (n=61) and 19% for nivolumab 3 mg/kg + ipilimumab 1 mg/kg q 3 weeks ×4 doses (n=54), with both of these combination arms being followed by nivolumab 3 mg/kg q 2 weeks as maintenance. Responses were reported in both platinum sensitive and resistant patients. Median durations of response were 7.7, 4.4 months and not reached, respectively for nivolumab 1/ipilimumab 3, nivolumab 3/ipilimumab 1 and nivolumab alone. Median progression free survivals (PFSs) were 2.6, 1.4 and 1.4 months, respectively and median overall survivals (OSs) were 7.7, 6 and 4.4 months, respectively (3,4). In both KEYNOTE-028 and Checkmate-032, the responses to immunotherapy were long-lasting, as seen in other malignancies. One year OS, including updated data from ASCO 2017, was 37% for pembrolizumab, 27% for nivolumab and 40% for nivolumab + ipilimumab (43% for nivolumab 1/ipilimumab 3 and 35% for nivolumab 3/ipilimumab 1) (2-4).

Given the numerical differences in efficacy endpoints between the groups in Checkmate-032 and KEYNOTE-028, can we conclude that one PD-1 inhibitor

drug is better than another, or that combination PD-1/CTLA-4 inhibition is better than PD-1 monotherapy? Not yet. KEYNOTE-028 was a small study with wider 95% confidence intervals around the ORR point estimate for monotherapy (15.6–55.3%) than around the ORR point estimate for nivolumab monotherapy in Checkmate-032 (5–18%). Equally, for the efficacy 'differences' between the monotherapy and combination arms in Checkmate-032 no statistical comparisons were made between the groups and the 95% confidence intervals for the ORRs of all three treatment groups overlapped (2-4).

Beyond the challenges of ascribing true differences between small populations, there were also differences in the patient populations included in the two trials. For instance, the relative percentage of CNS disease has not been reported in Checkmate-032 to date, whereas stable CNS disease was reported in 12.5% of KEYNOTE-028 (somewhat low for small cell). Consequently, whether there were more, similar or less rates of CNS disease in Checkmate-032 is not clear. Also, there were only 12.5% of patients in KEYNOTE-028 who had received only one prior systemic therapy (87.5% received ≥2 prior lines of therapy), while this percentage was 43% for Checkmate-032 (57% received ≥2 previous lines of treatment). Additionally, the relative percentages of platinum sensitive and resistant disease were not reported for KEYNOTE-028, whereas it was 42–50% platinum sensitive in the Checkmate-032 arms. Potential differences between tumor burden of target lesions and presence/absence of liver metastasis between trials have also not been reported, with these factors having been suggested in studies in other tumor types to influence response to immune checkpoint inhibitors (2-4).

Just as we have challenges in determining true differences in efficacy between the small groups available for analysis to date, similarly it is difficult to determine true differences in toxicity between the treatment approaches in these trials. In Checkmate-032 there was a numerically higher rate of severe toxicities with the two combination regimens compared to nivolumab monotherapy (grade 3 or 4 treatment-related adverse events occurred in 30% of patients with nivolumab 1/ipilimumab 3, 19% with nivolumab 3/ipilimumab 1 and 13% with nivolumab alone). Three cases of limbic encephalitis occurred (two in the nivolumab monotherapy cohort and one in the nivolumab 1/ipilimumab 3 cohort) and three treatment related deaths occurred [2 with nivolumab 1/ipilimumab 3 (from myasthenia and from renal failure) and 1 with nivolumab 3/ipilimumab 1 (from pneumonitis)] (3,4). In contrast, the incidence of grade 3–5 toxicities in the trial by Ott *et al.* was 33%, numerically higher than with nivolumab monotherapy. With pembrolizumab monotherapy there was one treatment related death due to colitis/intestinal ischemia (2).

In both the KEYNOTE-028 and Checkmate-032 trials, most patients did not respond, with non-responders progressing very rapidly and having poor outcomes. This is important to realize before PD-1 directed therapy is hailed as a panacea for all SCLC cases. In addition, perhaps due to the known propensity of SCLC to be associated with autoimmune paraneoplastic syndromes, some of the more unusual severe toxicities seen, notably the encephalitis and myasthenia, may give particular concern about immunotherapy treatment risks in this population. Thus, to improve the risk: benefit ratio, patient selection will be key. However, how we should do this remains uncertain.

In contrast to KEYNOTE-028, the Checkmate-032 study did not preselect patients based on PD-L1 staining, but it was assessed retrospectively (2-4). The percentage of screened patients staining positive for PD-L1 (≥1%) was 31.7% in KEYNOTE-028 and 18% in Checkmate-032, suggesting that SCLC tends to have a lower frequency of PD-L1 expression than non-small cell lung cancer (NSCLC) (2-6). While the pembrolizumab ORR among a PD-L1 preselected population was numerically higher than in the unselected Checkmate-032 population, retrospective analyses suggest PD-L1 staining ≥1% did not enrich for response in Checkmate-032 compared to <1%. Indeed, ORRs were actually higher among the PD-L1 negative group in Checkmate-032 (14% *vs.* 9% for nivolumab monotherapy; 32% *vs.* 10% for the nivolumab/ipilimumab combinations) (4). While different assays for PD-L1 were used in the two trials, comparison studies suggest their readouts should be similar (7).

If PD-L1 staining is not a good selection criteria for immune checkpoint inhibition in SCLC, then what is? High mutational load has been suggested to correlate with improved response and survival to immunotherapy in NSCLC. SCLC appears to have a similar mutational load as NSCLC (8). To date, in KEYNOTE-028 the data on mutational load and its association with response have not been provided (2). However, recently, data for tumor mutational burden (TMB) and its relationship to response in Checkmate-032 were presented. TMB in this study was determined by whole exome sequencing (WES) with groups divided into low, intermediate and high tertiles (9). For nivolumab monotherapy the ORR was 21% for those in

the high TMB group *vs.* 5% for the lowest TMB group, while for nivolumab + ipilimumab it was 46% *vs.* 22%. Median PFS confidence intervals of the different TMB subgroups within each treatment arm all overlapped, although landmark analyses suggested higher PFS rates at 12 months correlated with higher TMB. OS analyses had similar outcomes, although, in addition, the median values did appear to be significantly higher for high TMB in the combination arm, although not with monotherapy. The real applicability of such data to routine clinical practice remains uncertain. WES is costly and we are still studying how TMB predicted from targeted gene sequencing correlates with results from WES. In addition, no absolute values for 'high' TMB are being used, just relative values within a tumor type. As with other predictive markers for immunotherapy, no TMB group with guaranteed benefit or one completely devoid of benefit was identified. Of note, the ratio of response rate enrichment by TMB (from lowest to highest tertile) appeared much greater in the monotherapy group (21:5) than in the combination therapy group (46:22), possibly suggesting that one role of this assay might be to influence the decision on who needs combination immunotherapy *vs.* monotherapy, although the PFS and OS data are less clear cut on this issue.

Increased T-cell infiltrates within the tumor and at the invasive tumor margin have been associated with improved responses to immunotherapy in other tumor types. Whether this same relationship is present in SCLC is not known. While a smoking related gene signature has been suggested to predict response in some tumor types, this gene signature is unlikely to predict response among SCLC patients as almost all SCLC cases are smoking related, yet only a minority respond to immune checkpoint inhibition. Other potential predictive biomarkers to explore in SCLC include Myc amplification. Myc is amplified in 30 to 50% of human SCLC cell lines and in 19% of SCLC specimens (10). Myc signaling increases expression of PD-L1 and CD47 inhibitory immune checkpoints, and so should be explored as a predictor of immunotherapy benefit (11).

There are also many ongoing trials further exploring the potential for immunotherapy in SCLC. Current trials for extensive stage disease include those evaluating immune checkpoint inhibition in combination with, or as maintenance therapy after, first line chemotherapy; in combination with the DLL3-directed antibody drug conjugate rovalpituzumab tesirine; and in combination with radiation (NCT02538666, NCT02658214, NCT02701400, NCT02763579, NCT02934503, NCT03026166, NCT03041311, NCT03043599, NCT03043872, and NCT03066778). Given the recent positive results of durvalumab post-chemoradiation for stage III NSCLC within the PACIFIC trial, examination of PD-1 axis inhibition in a similar setting for limited disease SCLC will be important (12). Other future directions may include combinations of immune checkpoint inhibition with other immunomodulatory agents or with autologous T-cell therapy.

To date, the NCCN guidelines on SCLC have avoided specific recommendations with regard to nivolumab monotherapy versus nivolumab + ipilimumab in combination or any preferred dose/regimen of either drug. KEYNOTE-028 suggests pembrolizumab monotherapy might reasonably be added to the same list of next line agents to consider in SCLC, but with a continued lack of definitive data to issue a preference for one immunotherapy drug or regimen over another, or even whether PD-L1 staining should be used to select patients for such treatment. However, while more data are definitely required, the promise of immunotherapy in at least some patients with advanced SCLC appears real.

Acknowledgements

None.

Footnote

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

References

1. Small Cell Lung Cancer Guidelines Version 3.2017. Available online: http://www.nccn.org/professionals/physician-gls/pdf/sclc.pdf
2. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the Phase Ib KEYNOTE-028 study. J Clin Oncol 2017;35:3823-9.
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. Hellman MD, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort

from CheckMate 032. J Clin Oncol 2017;35:abstr 8503.
5. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med 2017;376:2415-26.
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
7. Scott ML, Ratcliffe MJ, Sharpe A, et al. Concordance of tumor cell (TC) and immune cell (IC) staining with Ventana SP142, Ventana SP263, Dako-28-8 and Dako-22C3 PD-L1 IHC tests in NSCLC patient samples. J Clin Oncol 2017;35,15:e14503.
8. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.
9. Antonia SJ, Callahan MK, Awad MW, et al. Impact of Tumor Mutation Burden on the Efficacy of Nivolumab or Nivolumab + Ipilimumab in Small Cell Lung Cancer: An Exploratory Analysis of CheckMate-032. Abstract 11063. Presented Oct 15-18, 2017. IASLC 18th World Conference on Lung Cancer, Yokohama, Japan.
10. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53.
11. Casey SC, Tong L, Li Y, et al. MYC regulates the antitumor immune response through CD47 and PD-L1. Science 2016;352:227-31.
12. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in Stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919-29.

Cite this article as: Pacheco JM, Camidge DR. KEYNOTE-028: how do we use immunotherapy in small cell lung cancer? Transl Lung Cancer Res 2017;6(Suppl 1):S84-S87. doi: 10.21037/tlcr.2017.10.02

