Editorial Commentary

On the precipice of a new generation of biomarkers for immunotherapy in small cell lung cancer

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After decades of stagnation, the addition of programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors to first-line chemotherapy for extensive-stage small-cell lung cancer (ES-SCLC) represented a new standard that improves survival outcomes and provides the possibility for a longer-term response. Whereas the management of non-small-cell lung cancer (NSCLC) has become more personalized as we have been able to divide the disease into multiple subtypes with distinct personalized therapies based on predictive biomarkers, biomarkers in ES-SCLC have been elusive and we continue to treat it as a single disease entity (1,2). The lack of biomarkers in ES-SCLC echoes the broader challenge of predicting outcomes with immune checkpoint inhibitor treatment across tumour types, where a small subset of patients that remain largely uncharacterized can derive significant benefits with deep and durable responses (3). In SCLC, the addition of atezolizumab or durvalumab to standard chemotherapy has improved overall survival (4,5). However, the three-year survival rates remain low at 16% and 17.6% respectively and the survival advantage seen in these trials is largely driven by a small population of patients experiencing lasting benefit (4,5). Moreover, unlike many other tumour types, dual checkpoint inhibition targeting both programmed cell death-1 (PD-1)/PD-L1 and CTLA4 has not emerged as a superior treatment strategy in ES-SCLC, and no predictive biomarkers for dual checkpoint inhibition exist (3).

Paz-Ares *et al.* (6) reported an exploratory biomarker analysis of the phase III CASPIAN trial evaluating the predictive role of PD-L1 expression and tumour mutation burden (TMB) in both single checkpoint blockade with durvalumab (D) and dual checkpoint blockade with durvalumab and tremelimumab (D + T) added to etoposide and platinum (EP) chemotherapy. The CASPIAN trial demonstrated that single checkpoint inhibition with D in addition to EP chemotherapy for the first-line treatment of ES-SCLC improved survival and established durvalumab as a standard of care in ES-SCLC alongside atezolizumab with EP chemotherapy. The D + T + EP arm of the trial underperformed relative to the D + EP arm and CTLA4 inhibition has yet to find a place in SCLC. In this analysis, Paz-Ares *et al.* (6) reported PD-L1 expression using the Ventana SP263 immunohistochemistry (IHC) assay in both tumour cells (TC) and tumour-associated immune cells (IC), defining positivity as staining in ≥1 cell. PD-L1 positivity has been found to be of relatively low prevalence in SCLC

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TC; IC are more likely to show expression of PD-L1, yet IC PD-L1 positivity is also observed only in the minority of SCLC tissue samples (7). Testing of tumour samples available from the CASPIAN study population was in keeping with this previous knowledge, revealing a prevalence of PD-L1 positivity in 5.7% of TC, 25.8% of IC and 28.3% in either TC or IC.

In the analysis of PD-L1 expression as a predictive biomarker, it was not found to be useful in predicting overall survival with the addition of D to EP with overall survival hazard ratios (HR) describing the benefit of adding D of 0.61 and 0.63 for PD-L1 positive and negative cohorts respectively (6). To put this finding in context, PD-L1 also failed to emerge as a predictive biomarker in two other large phase three ES-SCLC clinical trials in which a single anti-PD(L)1 agent was added to EP chemotherapy, IMPOWER 133 and KEYNOTE 604 (8,9).

While less clinically relevant, this analysis by Paz-Ares and colleagues did suggest, however, that PD-L1 expression may serve as a predictive biomarker for dual checkpoint inhibition. Specifically, in the cohort receiving D + T and EP, there were improved HRs seen with the addition of D and T in the PD-L1 ≥1 subgroup compared to the PD-L1 <1 subgroup based on TC (HR 0.42 *vs.* 0.76), IC (HR 0.53 *vs.* 0.88) and TC or IC (HR 0.50 *vs.* 0.91). As a *post-hoc* subgroup analysis with only 54.4% of the trial population having tissue that was suitable to evaluate biomarkers, these findings can only be considered hypothesis-generating. Given that D + T + EP is not a standard of care in ES-SCLC, the finding has minimal clinical relevance at present. Indeed, the Kaplan-Meier overall survival (OS) curves in the PD-L1 positive cohort are noted to cross, with the superiority of the D + T + EP only emerging after the 12-month mark. This may reflect the higher toxicity of the regimen with the addition of an anti-CTLA4 inhibitor (10), and demonstrates that further work is required if there is to be a biomarker-defined subset of ES-SCLC for whom dual immunotherapy with EP is appropriate. Our enthusiasm for this finding is also slightly dampened due to the previous PD-L1 biomarker analysis in the CheckMate 451 trial that found PD-L1 expression was not predictive of benefit from either single or dual immunotherapy checkpoint blockade (11). This disparate result does not necessarily conflict with the findings of the current analysis, however, as CheckMate 451 utilized single or dual checkpoint inhibition with nivolumab ± ipilimumab in the maintenance setting after response to chemotherapy and therefore showcases a different patient population in a different clinical scenario. However, this does reflect the complexity of a potential biomarker and the need for future research.

Since the publication of the current analysis, molecular transcription analysis of the CASPIAN trial by Xie and colleagues (12) has been published which further corroborates the findings of Paz-Ares *et al.* Over the past 5 years, research into the molecular signatures of SCLC has led to the emergence of four distinct molecular subtypes of SCLC: SCLC-A, N, P and I. The first three were each linked to overexpression of specific transcription factors, ASCL1, NEUROD1, and POU2F3 respectively, while SCLC-I is not associated with overexpression of those transcription factors but high IC infiltration and cytotoxic activity (13). This model has been validated by Gay *et al.* in an exploratory analysis of IMPOWER 133, where having SCLC-I subtype was found to be prognostic, although not predictive, of a good response to single immune checkpoint inhibition (13). Similar findings have been replicated by Xie *et al.* in the CASPIAN trial population as well, with further exploratory analysis in the dual checkpoint inhibition arm demonstrating the highest reported median survival of 30.8 months in the SCLC-I subgroup when treated with D + T + EP (12). However, due to the rarity of the subtype per the strict criteria, no statistical comparison could be done. Building on the work of Gay *et al.*, Xie *et al.* found RNA signatures of inflammatory responses that are associated with SCLC-I tumours that also predict good dual immune therapy response. In particular, the presence *vs.* absence of the T-cell inflamed RNA signature was found to have a statistically significant HR in OS of 0.36 in patients treated with D + T + EP, with a median survival of 30.8 months in patients with the T-cell inflamed signature receiving D + T + EP (12). Given the PD-L1 positive cohort is enriched with the SCLC-I subtype, the signal in PD-L1 positive subgroup seen in the Paz-Ares *et al.* analysis may be a reflection of the impact of SCLC-I and inflammatory signatures. This also provides a potential molecular mechanism for PD-L1 positivity as a biomarker predictive of benefit of dual checkpoint blockade, as the SCLC-I subtype is known to be correlated with increased expression of CD80 and 86 (13), the molecular targets of the CTLA4 receptor. Furthermore, in the previous analysis (13) of molecular subtypes, SCLC-I appears to be correlated to platinum resistance; the disparate result between CASPIAN and CheckMate 451 may be due to CheckMate 451 excluding patients with a more inflamed signature due to the trial design in which patients were only enrolled after they had exhibited an initial response to first-line platinum-based chemotherapy.

The analysis done by Paz-Ares *et al.* also included TMB, which was evaluable in 35.2% of the intention-to-treat (ITT) trial population. Although TMB has been extensively studied as a biomarker for checkpoint inhibitor response, its role has been inconsistent across tumour types and has previously been shown to have no predictive or prognostic value in an analysis of IMPOWER 133 (8,14) in the first-line setting for ES-SCLC, with Nabet *et al.* further demonstrating TMB being independent from the current understanding of molecular subtypes (14). This current analysis corroborates the previous finding with TMB having no impact on survival between treatment arms regardless of cutoff value while also demonstrating that TMB value and PD-L1 expression appear to be independent of each other, substantiating the hypothesis that PD-L1 and TMB may represent different independent aspects of the immune response and a deep understanding of immune response may require the understanding of multiple interacting factors (15,16). Indeed, in CheckMate 451, although the overall trial was negative and PD-L1 expression was not predictive of outcomes, analysis based on TMB showed a signal to be predictive of immunotherapy response (11). Therefore, while TMB was not shown to be a predictive biomarker in the CASPIAN population, further research into the interaction between TMB, molecular subtype and inflammatory signatures is needed.

The recent results published by Paz-Ares *et al.* further substantiate that PD-L1 and TMB are not the predictive biomarkers we seek in ES-SCLC. Furthermore, immune checkpoint inhibitors can cause unpredictable and potentially life threatening immune related adverse effects, and we are also far from biomarkers that could predict adverse events (17,18). However, the collaboration between clinical trials and translational biomarker research has provided the opportunity for a glimpse into a new generation of biomarkers. One of the major challenges in defining the best use of immunotherapy checkpoint inhibitors to improve outcomes in small cell lung cancer has been the relatively cold tumour microenvironment, and this has likely also informed the lack of utility of both PD-L1 and TMB as useful biomarkers. Specifically, SCLCs often feature decreased antigen presentation through downregulation or silencing of major histocompatibility complex (MHC) class I antigen processing and presentation, with 70–80% of SCLC tumour specimens showing loss of MHC class I expression (19). Thus, a high TMB may not translate into a higher number of neoantigens being presented to T cells. Further, SCLC has been shown to have a lower abundance of CD8 T cells in the tumour microenvironment compared to NSCLC, whereas populations of immunosuppressive IC are increased in SCLC (20,21). There are data emerging that suggest that useful biomarkers for SCLC will come from proteogenomic analysis that reflects the relative activity of these immunosuppressive processes (22,23), while metagenomic analysis may reveal the interplay of multiple factors in cancer immune response (24) and the future in therapy for SCLC may hinge on our ability to manipulate the cold tumour microenvironment into a hot one (25).

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Footnote

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