



## EDITORIAL

## Immunotherapy in refractory SCLC: the caterpillar struggling to become a butterfly



In the era of immunotherapy we got used to it very well discovering day by day positive results in different settings and diseases in particular non-small cell lung cancer, in which the use of different agents such as anti-programmed cell death protein 1 (PD-1), anti-programmed death-ligand 1 (PD-L1) and/or anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) increased significantly survival outcomes with durable disease remission.<sup>1</sup> The development of these new agents, benefited from the evolution of biomarker for patient's selection starting from PD-L1 up to the TMB, still under evaluation but with a consistent amount of data that are good for hope.<sup>2–4</sup>

Thanks to these driving clinical premises coming from the robust experience on NSCLC, the development of immune-checkpoint inhibitors (ICIs) moved to SCLC, also due to the biological rationale and its potential clinical use. Indeed, SCLC showed high association with smoking habit and high mutational burden, characterized by mutations in such tumour-suppressor gene as TP53 and RB1, Notch and MYC family members, often induced by tobacco carcinogens.<sup>5</sup> Considering these biological characteristics suggesting that SCLC may be highly immunogenic and could respond very well to ICIs, different randomized clinical trials (RCTs) were developed to investigate the role of these new agents for the treatment of extensive-stage small-cell lung cancer.<sup>5–7</sup>

Preliminary shreds of evidence supporting the activity of ICIs in relapsing SCLC were reported in phase I/II CheckMate 032 trials, evaluating nivolumab monotherapy and two dose levels of combined nivolumab and ipilimumab. In this trial, in which patients were eligible regardless tumour programmed death ligand 1 (PD-L1) expression, overall response rate (ORR) resulted in 10% in the nivolumab monotherapy arm and 19% in the combination.<sup>8</sup>

Based on these early and positive data, though based on an investigator assessment, FDA granted an accelerated approval to nivolumab for the treatment of patients with metastatic refractory SCLC in August 2018 and the NCCN guidelines recommend nivolumab ± ipilimumab as a new standard of care option. In particular, this new indication was based on the duration of response (DoR) achieved

in the CheckMate 032 trial, showing an ORR of 12% and a median DoR of 12.9 months, with 62% of patients responding at 12 months and 39% still responding at 18 months.

In addition to these efficacy achievements, this trial did not show a significant difference between positive ( $\geq 1$ ) and negative tumors for PD-L1 expression in terms of ORR and survival, unlike what happened in non-small cell lung cancer.<sup>9</sup>

Riding this wave, different randomized and non-randomized clinical trials starting to evaluate the role of ICIs as atezolizumab<sup>10</sup>, pembrolizumab<sup>11,12</sup> or durvalumab<sup>13</sup> in the same setting, showing not encouraging results, also in the PD-L1 enriched population. Atezolizumab was evaluated in the IFCT-1603 non-comparative phase II study, showing an ORR of 2.3% and progression-free survival (PFS) of 1.4 months.<sup>10</sup> Pembrolizumab, in the PD-L1 positive ( $\geq 1$ ) setting was investigated in two different trials of relapsing SCLC: the KEYNOTE 028 and the KEYNOTE 158, a very limited PFS of 1.9 and 2.0 months, respectively. Also, durvalumab failed to demonstrate an increase in survival in the same clinical set, achieving a PFS of 1.5 months and ORR 10%.<sup>11,12</sup>

Although these results were reported with high emphasis underlining the antitumor activity of ICIs in patients with pretreated or relapsed SCLC, in reality, failed to show the promising and heralded efficacy in this particular setting.

Nevertheless, these preliminary although unconvincing data, a randomized phase III trial (CheckMate 331) was conducted to evaluate nivolumab in monotherapy versus a standard second-line with either topotecan or amrubicin upon investigator's choice, in patients with relapsed SCLC following platinum-based chemotherapy, having an overall survival (OS) as a primary endpoint.<sup>14</sup> Although the results are not yet published in comprehensive form, a press release announced that the treatment with nivolumab did not improve overall survival, confirming the previous results achieved in the other phase I/II clinical trials, investigating the same topic.

Overall, these results confirmed that significant unmet needs remain unanswered, moving us to think if there is a really please for immunotherapy in relapsed SCLC.

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Despite biological background suggested us the potential role of ICI in this setting, tumour immune escape in SCLC remains a hurdle to effective treatment, worsen different mechanism including immunogenicity, antigen modulation and tumour-induced immune suppression results in therapy resistance.<sup>15</sup>

To better optimize results and improving the survival outcome of patients suffering from refractory SCLC, we need immune-biomarker based clinical trials, even if theoretically the biological premises would not require it. This is highly recommended due to SCLC presents a highly aggressive growth rate and "tying to believe" cannot be a winning philosophy, but a careful selection of patients guided by biomarkers can be the only driver that can lead us to see the light in this arduous path. Notwithstanding nowadays multiple immunotherapy trials are currently enrolling patients with SCLC in different stage and setting of disease, several presents the same bias and limited data about accurate and preplanned biomarkers selections.

The role of immunotherapy should be carefully considered in SCLC, also based on the results of combination treatment with atezolizumab plus standard platinum-based chemotherapy of IMpower 133 clinical trials, that although showing a statistically significant improvement for the combo arm, the median change in overall survival was only about 2 months (12.3 vs 10.3 months, HR 0.70;  $p=0.007$ ), completely different from the results achieved with immunotherapy in the other histology as adenocarcinoma or squamous cell carcinoma, confirming the high difference of biology among the different histology.<sup>16</sup> Despite this improvement, representing a meaningful advance in this extremely aggressive malignancy, suggest us to improve our research and patient's selection.

Hoping that there will be a safe harbor for second-line immunotherapy in the SCLC, nowadays this opportunity remains limited and cannot be considered a viable therapeutic option for our patients.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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