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Review

# Immune checkpoint blockade in small cell lung cancer

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ABSTRACT

Despite the highly immunogenic potential of small cell lung cancer (SCLC), progress in evaluating the therapeutic value of immune checkpoint agents has lagged behind that of non-small cell lung cancer. Results from a number of phase I-III clinical trials that specifically address the use of anti-PD-1, anti-PD-L1 and anti-CTLA-4 agents in SCLC have now been reported. This review will focus on the available evidence for immune checkpoint blockade in SCLC and review current biomarker strategies with the aim of providing perspective and interpretation of this data for clinical practice.

## 1. Introduction

Small cell lung cancer (SCLC) exhibits distinct clinical and pathological characteristics defined by aggressive, early metastasis and high rates of relapse and disease resistance despite initial chemo-sensitivity [1]. Concurrent chemoradiation (CRT) remains the standard of care for patients with limited-stage (LS)-SCLC [2,3] with the addition of prophylactic cranial irradiation (PCI) resulting in survival benefit and reduced incidence of cerebral metastasis [4]. Platinum chemotherapy in combination with etoposide is regarded as standard initial therapy in extensive-stage (ES)-SCLC [5,6]. Following first-line chemotherapy, consolidation thoracic radiotherapy may offer a survival advantage in selected patients with residual thoracic disease [7,8] whilst PCI in the ES-SCLC setting has a less certain impact on overall survival (OS) [9,10].

Inevitably, most patients with SCLC will progress following initial treatment. In the platinum resistant/refractory setting, a distinct lack of effective second-line therapy is available. [11] Topotecan, irinotecan, amrubicin and combination cyclophosphamide/doxorubicin/vincristine regimens all have reported activity in SCLC after progression during or after platinum-based chemotherapy however responses are modest with median survival typically less than 6 months [12–14].

An expanding body of data provides a strong rationale for the development of immune checkpoint blockade studies in SCLC. Led primarily by loss of function of *TP53 and RB1*, this genetic hallmark of SCLC results in a high frequency of non-synonymous somatic mutations within the tumour genome, measured as tumour mutational burden (TMB) [15–18]. In a number of tumour types including non-small cell lung cancer (NSCLC), urothelial carcinoma and head and neck cancer, high TMB has been identified as a potential predictive marker, enriching for improved response to immune checkpoint blockade [18–20]. Prognosis of SCLC has also been linked with surrounding immune cell activity with worse survival found in patients with higher FOXP3 + T cells infiltrates [21] and improved survival associated with high CD45 + T cells counts [22]. Clinical evidence of the immunogenicity of SCLC has also been observed by the occurrence of paraneoplastic syndromes resulting from immune-mediated responses that suggest pathologic interplay between the tumour and the immune system [23–25].

This narrative review will focus on reported clinical studies that evaluate PD-(L)1 and CTLA-4 immune checkpoint inhibitors in SCLC with an aim to provide perspective on how this data can be interpreted for clinical practice.

## 2. Immunotherapy trials in extensive-stage SCLC (ES-SCLC)

### 2.1. First-line treatment

Pre-clinical data showing that cytotoxic-induced release of tumour specific antigens promotes T-cell activation and immune-mediated apoptosis [26], provide a robust foundation for the study of combined chemotherapy and immune checkpoint blockade in SCLC.

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Anti-CTLA-4 monoclonal antibody, ipilimumab was the first immune checkpoint inhibitor to be evaluated in combination with chemotherapy for untreated ES-SCLC. Despite encouraging phase II data [27], the addition of ipilimumab (10 mg/kg) to carboplatin/etoposide (PE) failed to improve overall survival (OS), the primary endpoint, compared to PE alone (11 vs 10.9 months; HR 0.94; 95% CI 0.81–1.09, p = 0.38) in the phase III CA184-156 study (NCT01450761) [28]. A total of 1132 ES-SCLC patients were enrolled. Overall response rate (ORR) was 62% in both arms, similar to historical controls. One-year OS rate was 40% in both arms. Treatment discontinuation was higher in the ipilimumab arm (18% vs 2%) with immune-mediated diarrhoea and colitis cited as the most frequent cause. No pre-specified subgroup appeared to benefit from the addition of ipilimumab, in particular the HR of 1.58 (95% CI 1.02 to 2.44) favoured placebo in the subgroup (n = 100) of patients with CNS metastases at baseline.

The phase III IMpower133 study (NCT02763579) provides the most convincing evidence to date on the role of checkpoint inhibition for first-line ES-SCLC treatment [29]. This study randomised (1:1) 403 patients with untreated ES-SCLC to PE plus anti-PD-L1 antibody atezolizumab (1200 mg every 3 weeks) or placebo for 4 cycles followed by maintenance atezolizumab or placebo until disease progression or unacceptable toxicity. The co-primary endpoints were OS and progression free survival (PFS). Median PFS was 5.2 vs 4.3 months (HR 0.77, 95% CI 0.62- 0.96, p = 0.02) for atezolizumab and placebo arm, respectively. At interim analysis, patients in the atezolizumab arm had longer median OS (12.3 vs 10.3 months; HR 0.7 95%, CI 0.54-0.91, p = 0.007) and higher 1-year OS rate (51.7% vs 38.2%). Notably, the additional survival benefit of atezolizumab was observed later, with separation of the survival curves seen from 6 months onwards. Similar ORR was reported in both arms (60.2% vs 64.4%; atezolizumab and placebo arms respectively), demonstrating that response rate is not an exclusive surrogate for survival in this setting. Immune-related adverse events (irAEs) occurred in 39.9% of patients with rash and hypothyroidism being the most frequently reported irAEs. Higher rates of AEs leading to treatment discontinuation were reported in the atezolizumab arm (11.1% vs 3.1%). Patient reported outcomes (PROs) assessment indicated that patients in both treatment arms experienced early palliation of lung cancer symptoms [30]. Patients in the atezolizumab arm reported a sustained clinical benefit with patient-reported physical function and health-related quality of life maintained until Week 51 and Week 54, respectively.

Results from IMpower133 indicate that the addition of atezolizumab to platinum/etoposide results in an absolute median OS benefit of 2 months and a meaningful 14% improvement in absolute survival at 1-year. An exploratory analysis using a blood-based tumour mutational burden assay showed no survival benefit using prespecifed cut-offs of 10 and 16 mutations per megabase (mt/Mb). Therefore, in the absence of an informative biomarker, it remains unclear how to best select for patients who will benefit from the addition of atezolizumab in the first-line setting. Particularly in patients with central nervous system (CNS) disease, the efficacy of immunotherapy is uncertain. Notably IMpower133 mandated CNS imaging with either contrast enhanced CT or MRI at screening. Patients with untreated or symptomatic CNS metastasis were excluded from the study. In the small number of patients enrolled with treated CNS metastases (n = 35, 9%), no OS difference was observed between to the two arms (HR 1.07, 95% CI 0.47–2.43). Prophylactic cranial irradiation (PCI) was permitted on study and received by 22 patients (11%) in each arm, however the impact of this intervention on CNS disease-free interval has not been specifically reported.

### 2.2. Maintenance treatment

Maintenance anti-PD-1 agent pembrolizumab (200 mg every 3 weeks) did not improve PFS compared to historical controls in a single-arm phase II study (NCT02359019) of 45 patients with ES-SCLC achieving response or stable disease following 4–6 cycles of induction PE [31]. The primary endpoint of the study was PFS. Median PFS and OS were 1.4 and 9.6 months, respectively. 1-year OS rate was 37%, similar to 1-year OS rates reported in the CA184-156 trial and in the placebo arm of IMpower133. ORR was 11.1% (CR n = 1, PR n = 4) in a population with disease control following platinum-based chemotherapy.

The 3-arm phase III CheckMate 451 study (NCT02538666) evaluated nivolumab 240 mg monotherapy vs ipilimumab 3 mg/kg + nivolumab 1 mg/kg vs placebo as maintenance therapy in ES-SCLC following first-line chemotherapy [32]. Disappointingly, CheckMate-451 failed to meet its primary endpoint for median OS in the combination ipilimumab + nivolumab arm (n = 279) vs placebo arm (n = 275). Median OS was 9.2 vs 9.6 months (HR 0.92, 95% CI 0.75–1.12, p = 0.37), respectively. 1-year OS was 41% vs 40%. Formal analysis of OS in the nivolumab monotherapy vs placebo arms was not undertaken due to statistical hierarchy, although descriptively reported as 10.4 vs 9.6 months (HR 0.84, 95% CI 0.69–1.02).

Based on the current available evidence from first-line and maintenance trials (Table A1), the timing of checkpoint inhibition initiation appears important in order to gain an additional survival benefit above that of chemotherapy alone, perhaps due to the synergistic impact of cytotoxic-induced tumour antigen exposure timed concurrently with an enhanced T-cell-mediated anti-tumour response from PD-1/PD-L1 pathway inhibition. Although induction vs maintenance schedules have not been prospectively compared head-to-head, initiation of atezolizumab monotherapy with induction chemotherapy is the current favoured approach in ES-SCLC based on IMpower133 results reporting an OS survival advantage [29]. The addition of ipilimumab to induction chemotherapy offers no additional survival benefit in the first-line setting. At present, there is no biomarker or clinical features that can guide patient's selection for checkpoint inhibition in the first-line and maintenance ES-SCLC setting.

### 2.3. Second-line and beyond

CheckMate 032 (NCT01928394), an open label phase I/II study evaluated the anti-tumour activity of nivolumab alone or in combination with ipilimumab in recurrent SCLC following progression after at least one platinum-based regimen [33,34]. A total of 216 patients were assigned to one of four dosing schedules; nivolumab 3 mg/kg every 2 weeks (Nivo3, n = 98), ipilimumab 1 mg/kg + nivolumab 1 mg/kg (Ipi1/Nivo1, n = 3), ipilimumab 3 mg/kg + nivolumab 1 mg/kg (Ipi3/Nivo1, n = 61) or ipilimumab 1 mg/kg + nivolumab 3 mg/kg + (Ipi1/Nivo3, n = 54). All combination regimens were administered 3-weekly for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks. The primary end point, ORR, was 10% (n = 10/98) for Nivo3, 33% (n = 1/3) for Ipi1/Nivo1, 23% (n = 14/61) for Ipi3/Nivo1 and 19% (n = 10/54) Ipi1/Nivo3. A randomised expansion cohort of CheckMate 032 was then added, comparing Nivo3 vs Ipi3/Nivo1 treatment schedules. Within the randomised expansion cohort, a higher ORR was achieved in the combination arm (21%) compared to nivolumab monotherapy (12%).

Thus far, survival has only been reported in the non-randomised CheckMate 032 cohort where median OS was 7.8 months in the Ipi3/Nivo1 arm and 4.1 months in the Nivo3 arm. 1-year OS (40% vs 27%) and 2-year OS (26% vs 14%) were consistently improved in the combination arm [35]. Similar to a number of other checkpoint inhibitor studies, a plateau in the survival curves was observed in both arms indicating that a select subset of patients attain a durable clinical benefit. It must be emphasised that the non-randomised nature of these survival results do not allow for formal comparison across dosing cohorts and final results from the randomised cohort are awaited. Significantly, objective responses were observed in heavily pre-treated patients including 109 patients on third- or later-line nivolumab [36]. In this particular group, ORR was 11.9% and median PFS and OS were

1.4 and 5.6 months, respectively. Based on these findings, accelerated FDA-approval has been granted for single agent nivolumab for patients who experience progression after platinum-based chemotherapy and 1 other line of therapy.

However, the benefit of nivolumab following first-line platinum chemotherapy has been challenged by the results of the phase III CheckMate 331 study (NCT02481830) [37]. A total of 569 patients with relapsed SCLC following first-line platinum-based chemotherapy were randomised (1:1) to nivolumab (240 mg every 2 weeks) or chemotherapy (topotecan or amrubicin). Patients with platinum-sensitive disease represented over a half (56%) of the study population. No significant improvement in OS, the primary endpoint, was observed between the two arms; nivolumab 7.5 months vs chemotherapy 8.4 months (HR 0.86, 95% CI 0.72–1.04, p = 0.11). In this head-to-head study, PFS was shorter in the nivolumab arm compared to chemotherapy (1.4 vs 3.8 months; HR 1.41, 95% CI 1.18–1.69), although a similar ORR was achieved in both arms (nivolumab 13.7% vs chemotherapy 16.5%). A longer duration of response was observed in the nivolumab arm (8.3 vs 4.5 months) suggesting a selected subset of patients treated with nivolumab may achieve longer-term benefit. Subgroup analysis indicated a trend toward improved OS with nivolumab compared to chemotherapy in patients with platinum-refractory disease (7.0 vs 5.7 months, HR 0.71, 95% CI 0.59-0.95) and patients without liver metastases (11.2 vs 10.5 months, HR 0.75, 95% CI 0.59-0.95). No pre-specified biomarker analysis has been presented so far.

In the phase 2 IFCT-1603 study (NCT03059667), 73 patients were randomised (2:1) to receive atezolizumab (1200 mg every 3 weeks) or up to 6 cycles of chemotherapy (topotecan or re-induction of initial chemotherapy) [38]. The majority of patients had platinum-sensitive disease (64.4%). The primary end point, ORR at 6 weeks, was 2.3% vs 10% for the atezolizumab arm and chemotherapy arm, respectively. Median PFS was lower in the atezolizumab arm (1.4 vs 4.3 months; HR 2.26, 95% CI 1.3–3.93, p = 0.004). No significant difference in OS was detected (9.5 vs 8.7 months; HR 0.84, 95% CI 0.45–1.58, p = 0.6).

The efficacy of pembrolizumab monotherapy (200 mg every 3 weeks) was evaluated in KEYNOTE-158 (NCT02628067), a phase II basket study of 11 different tumour types including 107 patients with pre-treated advanced SCLC [39]. The primary endpoint ORR was 18.7% in the overall population. Median OS was 9.1 months (95% CI 5.7–14.6 months) whilst PFS was 2 months (95% CI 1.9–2.1 months).

The SCLC cohort of KEYNOTE-028 (NCT02054806), a phase Ib study, included 24 pre-treated SCLC patients with PD-L1 expression ≥1% within the tumour and stroma [40]. An higher dose of pembrolizumab (10 mg/kg every 2 weeks for 24 months) was administered compared to the dose used in KEYNOTE-158. The primary endpoints were safety and tolerability. Overall, pembrolizumab was well tolerated with no new safety signals observed. Two (8%) patients experienced a severe treatment related adverse event (asthenia and colitis). ORR was 33.3% with one complete response. Median PFS and OS were 1.9 months and 9.7 months, respectively.

With regards to other dual checkpoint inhibitor combinations, the multi-arm phase II trial BALTIC (NCT02937818) assessed the preliminary efficacy of anti PD-L1 agent durvalumab plus anti-CTLA4 agent tremelimumab in platinum refractory/resistant ES-SCLC [41]. Preliminary results from Cohort A (n = 21, durvalumab 1500 mg + tremelimumab 75 mg every 4 weeks for up to 4 months followed by durvalumab 1500 mg every 4 weeks) have been reported. ORR, the primary endpoint, was 9.5% with a disease control rate (DCR) at 12 weeks of 38.1% (n = 8/21). Median PFS was 1.9 months (CI 95% 1.8–4.3 months) with a 6 month PFS rate of 13.1%. Median OS and the 1-year OS rate were 6 months (95% CI 1.9–12.0 months) and 32.7%, respectively. TRAEs of any grade and grade ≥3 occurred in 47.6% (n = 10) and 9.5% (n = 2) of patients, respectively. One treatment-related death due to haemorrhagic enterocolitis was reported.

At present, there are no immune checkpoint agents approved for use in the second-line ES-SCLC setting. Data from the phase III CheckMate 331 and phase II IFCT-1603 study affirm that chemotherapy remains the standard of care on progression after one line of platinum-based chemotherapy. Notably, over half of the study population in both these trials had platinum-sensitive disease. At this present time, the only FDA approved checkpoint inhibitor in pre-treated (following at least two lines of therapy) SCLC is nivolumab, based on phase II CheckMate 032 data [36]. Subgroup analysis from CheckMate 331 is also suggestive that nivolumab is more beneficial after failure of chemotherapy with survival favoring the nivolumab arm in patients with platinum-resistant disease but not platinum-sensitive disease. Results from CheckMate 331 also suggest that a selected subset of patients achieve longer-term benefit from nivolumab as indicated by separation of the OS curve at 1-year, however further analyses is needed to help identify these patients.

At present, there is no clear evidence to recommend use of PD-(L)1/CTLA-4 combinations in pre-treated SCLC. Upcoming results of the randomised CheckMate 032 cohort may provide greater clarity on this issue.

## 3. Predictive biomarkers

The predictive value of PD-L1 expression and tumour mutational burden (TMB) has been demonstrated in some tumour types although small biopsy samples, standardisation in cut-off thresholds and technical reproducibility are major limiting factors when validating these biomarkers for the SCLC population [42]. Previous series report a considerably lower frequency of PD-L1 expression in SCLC compared to NSCLC [33,39,43–45].

At present, the use of PD-L1 expression and TMB as a predictive biomarker of response to checkpoint inhibitors remains investigational.

PD-L1 expression was also assessed in 148 of 216 (69%) evaluable patients in the non-randomised cohort of CheckMate 032, a phase I/II study evaluating nivolumab alone or in combination with ipilimumab in recurrent SCLC following progression after at least one platinum-based regimen [33]. Positive PD-L1 expression was defined as ≥1% staining of tumour cells only (Dako clone 28-8 assay). In this study, the proportion of patients with PD-L1 expression ≥1% was 17%. No association between PD-L1 expression and the primary endpoint, ORR was established in this study.

A number of other phase II/III studies have also included PD-L1 analysis, with most including PD-L1 expression on host cells in addition to tumour cell PD-L1 expression. A pre-planned exploratory analysis of the phase II KEYNOTE-158 population reported PD-L1 positive tumours (22C3 pharmDx assay), defined as a PD-L1 tumour proportion score (TPS) ≥1% staining of tumour cells and/or tumour infiltrating immune cells, in 42 (39%) patients [39]. In this population of pre-treated SCLC patients treated with pembrolizumab monotherapy, ORR was 35.7% vs 6% in the PD-L1-negative group. PD-L1 TPS expression appeared to predict for improved OS benefit (14.6 vs 7.7 months for PD-L1 positive and PD-L1 negative tumours, respectively). PD-L1 expression was not predictive for PFS, which was similar (2.1 vs 1.9 months) between the PD-L1 positive and PD-L1 negative groups.

In the single-arm phase II study of maintenance pembrolizumab following induction chemotherapy (NCT02359019), a modified tumour proportion score was used to assess PD-L1 expression for exploratory biomarker analysis [31]. The modified proportion score included both tumour cells and mononuclear cells staining for PD-L1 and PD-L1 expression was also assessed in the surrounding stromal interface. Tissue for PD-L1 expression assessment was adequate in 67% (n = 30/45) of patients. Positive tumour PD-L1 expression (≥1%) was only observed in 3 patients. Two patients with positive PD-L1 expression achieved partial response. Even fewer specimens were adequate for stromal PD-L1 expression, which was detected in 8 out of 20 (40%) assessable samples. Of these patients, median PFS and OS were 6.5 months (95% CI 1.1–12.8 months) and 12.8 months (95% CI 1.1–17.6 months) respectively, which was higher than the median OS reported in overall cohort.

PD-L1 analyses in the phase II IFCT-1603 study of atezolizumab vs chemotherapy (NCT03059667) [38] in pre-treated SCLC identified that only 1 out of 53 (2%) of evaluable specimens, had positive tumour cell PD-L1 staining (SP142 clone). When assessing PD-L1 on tumour-infiltrating immune cells, 16 patients were identified as having PD-L1 positive tumours however no significant difference in median PFS between immune score PD-L1 positive (n = 16) and immune score PD-L1 negative tumours (n = 39) were detected.

Given there are fundamental differences in the definition of PD-L1 expression between these trials, prospective evaluation and harmonisation are needed to demonstrate if PD-L1 expression holds any predictive value in SCLC treated with checkpoint inhibitors.

Tumour mutational burden (TMB) is an emerging biomarker independent to PD-L1 expression. At present, TMB appears to best select SCLC patients who will benefit from combination ipilimumab/nivolumab based on phase II Checkmate 032 data [46]. In this exploratory analysis, TMB was evaluated by whole exome sequencing in tumour samples. Of 401 patients in the intention-to-treat population, 211 (53%) had sufficient paired tumour material and whole blood samples for analysis, of which n = 133 received nivolumab alone and n = 78 received ipilimumab/nivolumab. Based upon the total number of non-synonymous somatic mutations, patients were categorised into 3 TMB categories; low (0–142 mut/Mb), medium (143–247 mut/Mb) and high (≥248 mut/Mb). In this exploratory analysis, high TMB was associated with near doubling of ORR compared to low/medium TMB in both the nivolumab monotherapy (21.3% vs 6.8% vs 4.8% for high, medium and low TMB, respectively) and ipilimumab/nivolumab (46.2% vs 16% vs 22.2% for high, medium and low TMB, respectively) treatment groups. ORR was higher among patient in the ipilimumab/nivolumab group vs nivolumab alone, in all TMB categories. In patients treated with ipilimumab/nivolumab, high TMB was associated with higher 1-year PFS rate (30% vs 8% vs 6.2% for high, medium and low TMB, respectively) and 1-year OS rate (62.4% vs 19.6% vs 23.4% for high, medium and low TMB, respectively). In patients with low or medium TMB, no considerable difference in 1-year PFS and 1-year OS rates between nivolumab and ipilimumab/nivolumab treatment groups was observed. Although exploratory, these results suggest that patients with high TMB are more likely to benefit from combination checkpoint blockade. Prospective validation and standardisation of assays is required before TMB could be implemented for routine clinical practice.

Blood-based plasma TMB has been examined as an exploratory biomarker given that scant/inadequate tissue sampling often limits assessment of tissue-based biomarkers eg. tissue TMB and PD-L1. Plasma TMB should be considered a separate biomarker entity to tissue TMB and concordance between tissue and plasma TMB assessment is not known. Blood-based plasma TMB was prospectively evaluated for exploratory biomarker analysis. In the first-line IMpower133 study [29]. Pre-specified thresholds of 10mut/Mb and 16 mut/Mb did not enrich for patients who would benefit from the addition of atezolizumab to platinum/etoposide as first-line ES-SCLC treatment.

## 4. Conclusions and future directions

For a small subset of patients, immune checkpoint blockade heralds a promising strategy for achieving disease control in SCLC. Based on IMpower133 data, there is clear evidence that the addition of atezolizumab to first–line carboplatin-etoposide chemotherapy prolongs OS over chemotherapy alone. Refining patient selection for those who will derive a survival benefit from combination atezolizumab/chemotherapy through a clinically validated biomarker remains one of the challenges ahead. Trials in progress that will add valuable understanding to the role of adding checkpoint inhibition to first-line chemotherapy include the phase II REACTION (NCT02580994) and phase III KEYNOTE-604 (NCT03066778) trials that will evaluate pembrolizumab/PE vs PE alone as well as the phase III CASPIAN (NCT03043872) study that will randomise between 3 arms; durvalumab/tremelimumab/PE vs durvalumab/PE vs PE alone.

Current data does not support the use of single-agent anti-PD-(L)1 (nivolumab, pembrolizumab, atezolizumab) in the second-line setting in an unselected population. In patients with pre-treated SCLC and high tumour TMB, the combination of ipilimumab/nivolumab heralds promising activity but, with the current lack of prospective randomised data available, chemotherapy remains the standard-of-care in pre-treated SCLC at present.

Given that the majority of patients with SCLC fail to respond to checkpoint inhibition alone, use of priming radiation and combining immunotherapy with targeted agents are two emerging strategies that aim to enhance an immune anti-tumour response.

The use of priming radiotherapy to enhance tumour antigen presentation, promote neoantigen formation and modify the tumour microenvironment in checkpoint inhibitor-treated patients [47] will be a strategy evaluated in ongoing trials including a phase II study (NCT02701400) of combination tremelimumab and durvalumab with or without radiotherapy and a single centre phase II study (NCT02934503) that will evaluate dynamic change in PD-L1 expression in ES-SCLC randomised to pembrolizumab in combination with chemotherapy +/- consolidation thoracic radiotherapy.

Limited-stage SCLC (LS-SCLC) represents an additional area of interest to evaluate synergistic impact of checkpoint agents and radiotherapy. Ongoing trials in LS-SCLC include the phase III ADRIATIC study (NCT03703297) that will investigate tremelimumab/durvalumab vs durvalumab + placebo vs placebo in patients with LS-SCLC following concurrent CRT and the phase II STIMULI (Small Cell Lung Carcinoma Trial with Nivolumab and IpiliMUmab in Limited Disease, NCT02046733) study that enrolls patients treated with concurrent CRT and randomises between induction ipilimumab 3 mg/kg + nivolumab 1 mg/kg followed by maintenance nivolumab 240 mg every 2 weeks for 12 months or observation. In addition, the phase II ACHILES study (NCT03540420) will evaluate 12 months of maintenance atezolizumab vs observation in LS-SCLC patients. Checkpoint inhibition initiated with concurrent CRT will be investigated in a single-arm phase II study (NCT03585998) of CRT + durvalumab followed by durvalumab consolidation for up to 2 years and in a single-centre phase I study (NCT02402920) of pembrolizumab with concurrent radiotherapy with or without chemotherapy in SCLC including a cohort of LS-SCLC patients.

Comprehensive genomic profiling has led to a greater understanding of the mutational landscape in SCLC [15] and represents an opportunity to define targetable aberrant molecular alterations that may have synergetic effect with checkpoint blockade. To this effect, a phase I/II trial (NCT03026166) will evaluate safety and efficacy of Rovalpituzumab-tesirine (Rova-T), an antibody drug conjugate targeting delta like protein 3 (DLL3) in combination with nivolumab or ipilimumab/nivolumab. Preliminary data suggest that the combination of Rova-T with nivolumab (Rova-T 0.3 mg/kg every six weeks for 2 cycles + nivolumab 360 mg every 3 weeks for 2 cycles then nivolumab 480 mg every 4 weeks until progression) was tolerable, with an ORR of 23%. Median PFS and OS was 4.8 m and 7.2 m respectively. Recruitment was terminated early after 12 patients due to dose limiting toxicities (DLT) in the Rova-T with nivolumab/ipilimumab cohort [48].

Preclinical data from immune-competent SCLC *in vivo* models also suggests that targeting DNA damage response (DDR) with poly ADP-ribose polymerase PARP inhibitor olaparib and checkpoint kinase 1 (CHK1) inhibitor prexasertib leads to activation of the innate immune STING/TBK1/IRF3 pathway and when combined with PD-L1 blockade, PARP and CHK1 inhibition results in increased cytotoxic T-cell infiltration and enhanced effect of PD-L1 blockade [49]. These findings support further investigation of the use of DDR inhibitors as a means to potentiate immune checkpoint responses in SCLC.

In summary, immune checkpoint inhibition represents a promising strategy to improve long-term survival in a very poor prognostic disease. Future endeavours to refine patient selection, validate predictive

**Table A1**
Results of trials evaluating PD-(L)1 and CTLA-4 blockade in ED-SCLC.

| Trial | Phase | N | Primary EP | Drug | mOS (HR, 95% CI) | mPFS (HR, 95% CI) | ORR |
|---|---|---|---|---|---|---|---|
| *First-line* | | | | | | | |
| **IMpower133** (NCT02763579) | III | 403 | OS PFS | Atezolizumab 1200 mg q3w + PE vs Placebo + PE | 12.3 m vs 10.3 m HR 0.7 (95% CI 0.54-0.91, p = 0.007) | 5.2 m vs 4.3 m HR 0.77 (95% CI 0.62-0.96, p = 0.02) | 60% vs 64% |
| **CA184-156** (NCT01450761) | III | 1132 | OS | Ipilimumab 10 mg/kg q3w x4, 10 mg/kg q12w + PE vs Placebo + PE | 11 m vs 10.9m HR 0.94 (95% CI 0.81-1.09, p = 0.38) | 4.6 m vs 4.4 m HR 0.85 (95% CI 0.75-0.97, p = 0.02) | 62% vs 62% |
| *Maintenance* | | | | | | | |
| **CheckMate 451** (NCT02538666) | III | 834 | PFS | Nivolumab 240 mg q2w vs Ipilimumab 3 mg/kg + nivolumab 1 mg/kg q3w, maintenance nivolumab 240 mg q2w vs Placebo | 10.4 m vs 9.2 m vs 9.6 m *Ipi/Nivo vs placebo: HR 0.92 (95% CI 0.75-1.12, p = 0.37)* | 1.9m Vs 1.7m Vs 1.4 m *Ipi/Nivo vs placebo: HR 0.72 (95% CI 0.6-0.87, p = NR)* | NR |
| **NCT02359019** | II | 45 | PFS | Pembrolizumab 200 mg q3w | 9.6 m | 1.4 m | 11.1% |
| Second-line | | | | | | | |
| **CheckMate 331** (NCT02481830) | III | 569 | OS | Nivolumab 240 mg q2w vs Topotecan or amrubicin | 7.5 m vs 8.4 m HR 0.86 (95% CI 0.72-1.04, p = 0.11) | 1.4 m vs 3.8 m HR 1.41 (95% CI 1.18-1.69, p = NR) | 14% vs 17% |
| *Second-line and beyond* | | | | | | | |
| **IFCT-1603** (NCT03059667) | II | 73 | ORR | Atezolizumab 1200 mg q3w vs Topotecan or re-induction initial chemotherapy | 9.5 m vs 8.7m HR 0.84 (95% CI 0.45-1.58, p = 0.6) | 1.4 m vs 4.3 m HR 2.26 (95% CI 1.3-3.93, p = 0.004) | 2.3% vs 10% |
| **CheckMate 032** (NCT01928394) Extended follow-up non-randomised cohort | I/II | 159 | ORR | Nivolumab 3 mg/kg q2w (n = 98) | 4.1m | NR | 11% |
| | | | | Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg q3w x4, maintenance Nivolumab 3 mg/kg q2w (n = 61) | 7.8 m | NR | 23% |
| **KEYNOTE-158** (NCT02628067) | II | 107 | ORR | Pembrolizumab 200 mg q3w | 9.1m | 2 m | 18.7% |
| **KEYNOTE-028** (NCT02054806) | Ib | 24 | Safety | Pembrolizumab 10 mg/kg q2w | 9.7m | 1.9m | 33.3% |
| **BALTIC** (NCT02937818) | II | 21 | ORR | Durvalumab 1500 mg + temelimumab 75 mg q4w, maintenance durvalumab 1500 mg q4w | 6 m | 1.9m | 9.5% |

EP: Endpoint; PFS: progression free survival; OS: overall survival; ORR: Objective response rate; PE: platinum/etoposide; NR: not reported.

**Table A2**
Trials ongoing investigating PD-(L)1 and CTLA-4 blockade in SCLC patients.

| Trial | Phase | Design | Primary endpoint |
|---|---|---|---|
| *Extensive-disease SCLC – trials ongoing* | | | |
| **First-line** | | | |
| **REACTION** NCT02580994 | II | Pembrolizumab + PE vs PE alone | PFS |
| **KEYNOTE-604** NCT03066778 | III | Pembrolizumab + PE vs Placebo + PE | PFS, OS |
| **CASPIAN** NCT03043872 | III | Durvalumab + Tremelimumab + PE vs Durvalumab + PE Vs PE | PFS, OS |
| NCT02934503 | II | Cohort A: Pembrolizumab + PE followed by RT Cohort B: Pembrolizumab + PE +/- RT Cohort C: PE followed by Pembrolizumab Cohort D: PE + RT followed by Pembrolizumab | Change in PD-L1 status |
| **Second-line and beyond** | | | |
| NCT02701400 | II | Durvalumab + Tremelimumab Vs Durvalumab + Tremelimumab + RT (SBRT or hypofractional RT) | PFS, ORR |
| NCT03026166 | I/II | Rova-T + Nivolumab Vs Rova-T + Nivolumab (various doses) + Ipilimumab 1 mg/kg Vs Rova-T + Nivolumab (various doses) + Ipilimumab 3 mg/kg | DLT |
| *Limited-Disease SCLC – trials ongoing* | | | |
| **ADRIATIC** NCT03703297 | III | Consolidation Durvalumab + placebo Vs Consolidation Durvalumab + Tremelimumab Vs Placebo | PFS, OS |
| **STIMULI** NCT02046733 | II | Consolidation Nivolumab + Ipilimumab Vs Observation | PFS, OS |
| **ACHILES** NCT03540420 | II | Consolidation Atezolizumab Vs Observation | 2 year OS rate |
| NCT03585998 | II | Concurrent CRT + Durvalumab followed by Durvalumab consolidation | PFS |
| NCT02402920 | I | Concurrent CRT + Pembrolizumab followed by Pembrolizumab consolidation | MTD |

PE: platinum/etoposide PFS: progression free survival OS: overall survival RT: radiotherapy SBRT: stereotactic body radiation therapy ORR: Objective response rate Rova-T: Rovalpituzumab Tesirine DLT: dose limited toxicities CRT: Concurrent chemoradiotherapy MTD: Maximum tolerated dose.

biomarkers and discover mechanisms to overcome immune-resistance are the challenges ahead in this field.

## Declaration of Competing Interest

R Tay: none

D Heigener: none

M Reck has received honoraria for lectures and consultancy from Abbvie, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, Celgene, Lilly, Merck, MSD, Novartis, Pfizer, Roche.

R Califano has received honoraria for consultancy, speaker's bureau and advisory board from Roche, BMS, MSD and Astrazeneca/ Medimmune

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## Appendix A

See Table A2

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