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REVIEW

First-line immune checkpoint inhibitors for extensive stage small-cell lung cancer: clinical developments and future directions

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Small-cell lung cancer (SCLC) is an aggressive and rapidly growing disease with poor prognosis. Despite intense efforts to improve clinical outcomes, platinum/etoposide chemotherapy has remained the most effective regimen for first-line extensive disease SCLC for decades. The addition of immune checkpoint inhibitors, and specifically programmed death-ligand 1 inhibitors, to standard platinum/etoposide, significantly improves survival and represents a promising advance in this field. However, identification of a predictive biomarker to refine patient selection is an area of unmet need. Further understanding of tumour immunity and mechanism of resistance is required to design novel strategies that improve survival. In this review, we describe recent developments and future directions on first-line immune checkpoint blockade for extensive disease-SCLC.

Key words: small-cell lung cancer, immune checkpoint inhibitors, lung cancer, atezolizumab, durvalumab

INTRODUCTION

Small-cell lung cancer (SCLC) accounts for about 15% of all lung cancers and represents one of the most aggressive malignancies associated with a fast tumour growth rate, early metastatic spread to distant sites and a strong association with tobacco.[1-4] About 70% of patients present with extensive disease SCLC (ED-SCLC) where the treatment intent is palliative and the 5-year overall survival (OS) rate poor (about 2%).[5] For more than 30 years, chemotherapy (ChT) with platinum and etoposide (PE) remained the front-line standard of care regimen for ED-SCLC. This induces high overall response rates (ORR) (60%-80%) but eventually all patients will progress and die of this disease.[6,7] Disease relapse usually happens within 3-6 months since completion of ChT and median OS is approximately 10-11 months, illustrating the need for new, innovative and effective therapy options for ED-SCLC.[8,9]

SCLC is a neuroendocrine tumour frequently associated with paraneoplastic syndromes, such as hypercalcaemia, syndrome of inappropriate antidiuretic hormone secretion, Cushing syndrome, Myasthenia gravis, Lambert-Eaton-syndrome, etc.[10] The increased incidence of paraneoplastic autoimmune phenomena suggests that SCLC is an immunogenic disease and therefore potentially a good candidate for treatment with immune checkpoint inhibitors (ICI). Of note, neurological paraneoplastic syndromes are associated with better disease outcome in patients with SCLC.[11] However, other paraneoplastic entities, such as Cushing syndrome, have been reported in clinically aggressive forms of carcinoid tumours.[12] Furthermore, SCLC proved to have increased genomic instability with a high tumour mutational burden (TMB) and neoantigen load, both potentially drivers of inmunogenicity.[13,14] By contrast, tumour infiltrating lymphocytes (TILS) seem to be less frequent in SCLC, potentially reflecting a low major histocompatibility complex (MHC) class I protein expression on SCLC cells and leading to a more immunosuppressive tumour environment.[15,16] Additionally, the expression of programmed death-ligand 1 (PD-L1) in tumour cells, a biomarker that positively correlates with ICI activity in non-SCLC (NSCLC), tends to be low in SCLC patients. The majority of genomic alterations described in SCLC are gene deletions, amplification or mutations in tumour suppressor genes which are less likely to generate immunogenic neoantigens.[13,14]

ICI have proven limited activity in advanced SCLC; nivolumab and pembrolizumab are currently approved by the US Food and Drug Administration as third-line options. Nivolumab was granted approval on the basis of the CheckMate-032 study demonstrating an ORR of 12% and a durable response for $\geq$12 months in 62% of the study population.[17,18] In June 2019, pembrolizumab was approved due to the activity shown in the Keynote-158 and

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-028 studies demonstrating an ORR of 19% and a duration of responses for ≥12 months in 68% of patients.[19,20]

SCLC cells have the potential to reduce MHC antigen expression and to inhibit TILS inducing an immunosuppressive tumour milieu. By contrast, cytotoxic ChT is able to induce an immunogenic cell death, leading to cross-presentation of tumour antigens to T-cells. Combining ICI with ChT, therefore, might counteract immune suppressive tumour mechanisms and restore immune responses.[21]

Most recently, several trials have investigated the blockade of the cytotoxic T-lymphocyte-associated protein 4 and PD-L1 (CTLA-4/PD-L1) axis in addition to standard PE or as maintenance therapy (Table 1). Results from two randomised clinical trials of PE in combination with PD-L1 inhibitors have shown unprecedented efficacy outcomes representing the first improvement in decades for SCLC patients, and have led to regulatory approval of atezolizumab and durvalumab.

In this manuscript we review recently presented first-line clinical trials evaluating immune checkpoint blockade for ED-SCLC and discuss future directions in this field.

ICI: A FIRST-LINE TREATMENT

Ipilimumab (CTLA-4 inhibitor) plus ChT

Ipilimumab was first investigated in a phase II study that randomised 130 patients to receive carboplatin/paclitaxel plus ipilimumab or placebo (in a phased or concurrent fashion).[22] In the concurrent arm, ipilimumab was administrated concurrently with ChT, allowing ipilimumab to be present at the earliest phase of ChT-induced antigen release. In the phased arm, two cycles of ChT were given alone followed by up to four cycles of ipilimumab plus ChT, allowing for antigen release to occur before ipilimumab exposure. The rationale to investigate these two alternative regimens is based on prior observations suggesting that the timing of ChT relative to ICI could impact outcome. The primary endpoint of immune-related progression-free survival (irPFS) was 5.3, 6.4 and 5.7 months in the control, phased and concurrent arm, respectively. There was an improvement in irPFS in the phased versus control arms [hazard ratio (HR) 0.64; $P = 0.003$], but not according to modified World Health Organization criteria: 5.22 versus 5.19 months [HR 0.93, 95% confidence interval (95% CI) 0.59-1.45; $P = 0.37$]. No significant improvement was observed in OS; the HR values relative to control were 0.75 (95% CI 0.46-1.23; $P = 0.13$) in the phased arm and 0.89 (95% CI 0.59-1.54; $P = 0.41$) in the concurrent arm. The ICE study was a single-arm, phase II study evaluating carboplatin/etoposide for six cycles with concurrent ipilimumab given on cycles 3-6 and every 12 weeks.[23] The primary endpoint of 1-year progression-free survival (PFS) was not met. Interestingly, survival exceeded historical data with a median OS of 17 months (95% CI 7.9-24.3) and 1-, 2- and 3-year OS rates of 56%, 29% and 10%, respectively. According to an *ad hoc* analysis, the autoimmune profile at baseline predicted better outcomes and a higher risk of neurological toxicity. Patients with any positive autoantibody detected at baseline experienced a significantly longer median PFS (8.8 versus 7.3 months; $P = 0.036$) and a trend to longer OS (18.5 versus 17 months; $P = 0.144$). Antinuclear antibodies positivity predicted for a significantly longer PFS (10.2 versus 6.9 months; $P = 0.032$). Three out of 15 patients with positivity for SOX2 and/or anti-Hu antibodies presented ipilimumab-related grade ≥3 or neurological toxicity, compared with none of 23 patients with negativity for these antibodies ($P = 0.054$). The incidence of grade ≥3 adverse events (AEs) was higher than expected (69%), and there were five treatment-related deaths. The authors concluded that ipilimumab could be beneficial in a subgroup of patients and recommended its use in a phased fashion to reduce toxicity. A subsequent phase III study randomised 1132 patients to receive four cycles of PE with phased ipilimumab or placebo and did not show any differences in OS (11.0 versus 10.9 months, HR 0.94, 95% CI 0.81-1.09; $P = 0.3775$) for ipilimumab and placebo, respectively, but resulted in a significant increase in AEs.[24]

Atezolizumab (anti-PD-L1) plus carboplatin/etoposide

The phase III trial IMpower133 randomised (1 : 1) 403 treatment-naive ED-SCLC patients with a performance status (PS) of 0-1 to receive PE (only carboplatin allowed) plus atezolizumab or placebo.[25] After four cycles of induction treatment, patients went on to receive maintenance treatment with atezolizumab/placebo until disease progression or loss of clinical benefit. Prophylactic cranial irradiation (PCI) was allowed as per the local standard of care whilst consolidation thoracic radiotherapy was not permitted. Co-primary endpoints were OS and investigator-assessed PFS. At a median follow-up of 13.9 months, the median OS was 12.3 months in the atezolizumab-PE group and 10.3 months in the placebo-PE group (HR 0.70, 95% CI 0.54-0.91; $P = 0.007$) and median PFS was 5.2 and 4.3 months (HR 0.77, 95% CI 0.62-0.96; $P = 0.02$), respectively. An updated efficacy analysis presented at the 2019 European Society of Medical Oncology (ESMO) annual meeting demonstrated a sustained OS benefit (12.3 versus 10.3 months, HR 0.76, 95% CI 0.60-0.95; $P = 0.015$) favouring the atezolizumab-PE arm. This led to an increase of the 12- and 18-month OS rate from 39.0% to 51.9% and 21.0% to 34%, respectively. Some 54.7% of patients treated in the atezolizumab-PE arm and 61.9% of patients treated in the placebo-PE arm received subsequent treatment. Notably, only 8.4% of patients randomly allocated to the placebo arm received ICI in a later line. ORR was similar (64.4% versus 60.2%) between the two arms.[26] The treatment-related discontinuation rates were 12.1% and 3.1% for the atezolizumab and placebo arms, respectively. Tolerability was comparable in both treatment groups with no concerning safety signals identified in the atezolizumab-treated population. A health-related quality of life (HRQoL) analysis based on patient-reported outcomes (PROs) showed that function and HRQoL improved in both arms after initiating treatment, with more pronounced and persistent HRQoL improvements in the atezolizumab arm.[27]

Table 1. Summary of trials in first-line and/or maintenance setting for extensive stage small-cell lung cancer

Trial ID	Phase	*N*	Study design	Treatment	Endpoint	PFS	OS
First-line trials							
NCT00527735	II	130	Randomised, double-blind to assess Ipi in combination plus ChT	Arm A (concurrent): Ipi + ChT × 4C → ChT × 2C Arm B (phased): ChT × 2C → Ipi + ChT × 4C Control arm: ChT + placebo × 4-6C	irPFS	5.7, 6.4, 5.3 mo[a] (A, B, control) HR 0.93; $P = 0.37$ (A versus control) HR 0.64; $P = 0.03$ (B versus control)	9.1, 12.9, 9.9 mo (A, B, control) HR 0.95, $P = 0.41$ (A versus control) HR 0.76, $P = 0.13$ (B versus control)
NCT01331525 (ICE)	II	42	Open-label, single-arm to evaluate Ipi in combination plus PE	Arm A: PE (up to 6C) + Ipi	1-year PFS	6.9 mo 1 year-PFS 15.8%	17.0 mo
NCT01450761	III	1132	Randomised, double-blind of phased Ipi plus PE	Arm A: PE × 4C + phased Ipi × 4C Control arm: PE × 4C + phased placebo × 4C	OS	4.6 versus 4.4 mo HR 0.85, $P = 0.0161$	11 versus 10.9 mo HR 0.94, $P = 0.3775$
NCT02763579 (IMpower133)	III	403	Randomised trial, double-blind of PE + atezolizumab or placebo	Arm A: PE + atezolizumab × 4C → atezolizumab Control arm: PE + placebo × 4C → placebo	PFS, OS	5.2 versus 4.3 mo HR 0.77, $P = 0.02$	12.3 versus 10.3 mo HR 0.70, $P = 0.007$
NCT03043872 (CASPIAN)	III	805	Randomised trial, open-label of PE with/out durvalumab and tremelimumab	Arm A: durvalumab + tremelimumab + EP × 4C → durvalumab + tremelimumab Arm B: durvalumab + EP × 4C → durvalumab Control arm: EP for up to 4C	OS	5.1 versus 5.4 mo (B versus control) HR 0.78; *P* not tested 4.9 versus 5.4 mo (A versus control) HR, 084 *P* not tested	12.9 versus 10.5 mo (B versus control) HR 0.75, $P = 0.0032$ 10.5 versus 10.4 mo (A versus control) HR 0.82, $P = 0.0451$
NCT03066778 (KEYNOTE-604)	III	453	Randomised, double-blind, placebo-controlled of PE with/out pembrolizumab	Arm A: pembrolizumab + PE Control arm: PE + placebo	PFS, OS	4.5 versus 4.3 mo HR 0.75, $P = 0.0023$	10.8 versus 9.7 mo HR, 0.80; $P = 0.0164$[b]
NCT03382561 (ECOG-ACRIN EA5161)	II	160	Randomised, open-label of PE with/out nivolumab	Arm A: PE + nivolumab × 4C → nivolumab Control arm: PE	PFS	5.5 versus 4.7 mo HR 0.68 $P = 0.0047$	11.3 versus 8.5 mo HR 0.67 $P = 0.038$
Maintenance trials							
NCT02359019	II	45	Open-label, single-arm study of pembrolizumab maintenance in patients not progressing to PE	Arm A: pembrolizumab × 2 years	PFS	1.4 mo	9.0 mo
NCT02538666 (Check-Mate 451)	III	834	Double-blind study of nivolumab + Ipi versus nivolumab versus placebo as maintenance in patients not progressing to PE	Arm A: nivolumab + Ipi × 4C → nivolumab × 2 years Arm B: nivolumab × 2 years Control arm: placebo × 2 years	OS	1.7 versus 1.4 mo (A versus control) HR 0.72 1.9 versus 1.4 mo (B versus control) HR 0.67	9.2 versus 9.6 mo (A versus placebo) HR 0.92; $P = 0.3893$ 10.4 versus 9.6 mo (B versus control) HR 0.84 (*P* not tested)

C, cycles; ChT, chemotherapy; HR, hazard ratio; Ipi, ipilimumab; irPFS, immune-related progression-free survival; mo, months; OS, overall survival; PE, platinum and etoposide; PFS, progression-free survival.

[a] irPFS.

[b] Superiority threshold $P = 0.0128$.

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Durvalumab (anti-PD-L1) with/out tremelimumab (anti-CTLA-4) plus PE

In the CASPIAN trial, 805 patients with treatment-naive ED-SCLC were randomly assigned (1 : 1 : 1) to receive four to six cycles of PE (carboplatin or cisplatin plus etoposide), up to four cycles of PE plus durvalumab followed by durvalumab maintenance or up to four cycles of PE plus durvalumab plus tremelimumab (anti-CTLA-4) followed by durvalumab maintenance.[28] PCI was only allowed in the control arm and given at the investigator's discretion, whilst consolidation thoracic radiotherapy was not permitted in any of the three arms.

In a pre-planned interim analysis, OS (primary endpoint) was longer in the durvalumab-PE arm versus the PE arm (13.0 versus 10.3 months, HR 0.73, 95% CI 0.59-0.90; $P = 0.0047$), translating into an improvement of the 12- and 18-month OS rate from 39.8% to 53.7% and from 24.7% to 33.9%, respectively. PFS did not differ between the arms (5.1 versus 5.4 months, HR 0.78, 95% CI 0.65-0.95 for durvalumab-PE and PE, respectively). Differently from IMpower133, this study showed higher confirmed ORR: 68% versus 58% (odds ratio 1.56, 1.10-2.22) for durvalumab-PE and PE, respectively. Notably, CASPIAN was an open-label study and responses were investigator-assessed, which may be a possible explanation for the higher ORR. Updated findings presented at the 2019 ESMO annual meeting[29] demonstrated that patients in the durvalumab-PE arm had a lower incidence of new lesions at first progression (41.4% versus 47.2%), whereas progression in target and non-target lesions was similar between arms (42.7% versus 39.4% and 24.6% versus 22.7%). An additional QoL analysis looking at PROs indicated a longer time to deterioration with durvalumab-PE based on favourable HR for all evaluated symptoms.

A recent update during the 2020 American Society of Clinical Oncology (ASCO) meeting[30] showed, with a median follow up of more than 2 years, a sustained OS improvement (12.9 versus 10.5 months, HR 0.75, 95% CI 0.62, 0.91; $P = 0.0032$) for durvalumab-PE versus PE. However, the addition of tremelimumab to durvalumab-PE (doublet ICI-PE) did not improve OS (10.5 versus 10.4 months, HR 0.82, 95% CI 0.68-1.00; $P = 0.0451$) as it did not meet the prespecified threshold for statistical significance of $P \leq 0.0418$. Moreover, no significant improvement was seen in PFS (4.9 versus 5.4 months, HR 0.84, 95% CI 0.70-1.01) and ORR (58.4% versus 58.0%) compared with PE alone. The OS rates at 18 and 24 months were 32.0% versus 30.7% versus 24.8% and 22.2% versus 23.4% versus 14.4%, for durvalumab-PE, doublet ICI-PE and PE, respectively. The rates of grade 3-4 AEs and AEs leading to treatment discontinuation were higher (70.3% and 21.4% versus 62.3% and 10.2% versus 62.8% and 9.4%) in the doublet ICI-PE arm compared with durvalumab-PE and PE. Treatment-related deaths occurred in 12 patients in the doublet ICI-PE arm, 6 in the durvalumab-PE arm and 2 in the PE arm. At baseline, 28 (10.4%) patients in the durvalumab-PE arm and 27 (10.0%) patients in the PE arm had known brain metastases, and only three patients in each arm received radiotherapy to the brain.[31] OS was improved with durvalumab-PE in patients with (HR 0.69, 95% CI 0.35-1.31) and without (HR 0.74, 95% CI 0.59-0.93) brain metastases. Among patients without brain metastases at baseline, a similar proportion (8.3% versus 9.5%) developed new brain metastases at first PD in the durvalumab-PE and PE arms, despite 19 (7.9%) patients in the PE arm receiving PCI.

Pembrolizumab (anti-PD-1) plus PE

KEYNOTE-604 is a phase III study that randomised 453 patients with ED-SCLC to receive PE (carboplatin or cisplatin) plus pembrolizumab or placebo for 4 cycles followed by pembrolizumab or placebo for up to 31 cycles.[32] PCI was given to 27 (11.8%) and 32 (14.2%) patients in the pembrolizumab-PE and PE groups, respectively. Primary endpoints were OS and PFS by blinded independent review.

In a prespecified interim analysis for PFS, pembrolizumab-PE modestly prolonged PFS (4.5 versus 4.3 months, HR 0.75, 95% CI 0.61-0.91; $P = 0.0023$). Interestingly, PFS curves overlap throughout the duration of ChT determining similar median PFS. After discontinuation of ChT, the curves diverge in favour of pembrolizumab-PE (12-month PFS rate of 13.6% versus 3.1%). In the final analysis, PFS benefit was maintained (HR 0.73, 95% CI 0.60-0.88), and the 12- and 18-month PFS rates were 15.9% versus 5.0% and 10.8% versus 2.1% for pembrolizumab-PE and PE, respectively. OS was numerically higher in the experimental arm (10.8 versus 9.7 months, HR 0.80, 95% CI 0.64-0.98; $P = 0.0164$) but did not reach statistical significance. The 12- and 18-month OS rates were 45.1% and 22.5% versus 39.6% and 11.2% for pembrolizumab-PE and PE, respectively. ORR was 70.6% and 61.8% for the pembrolizumab-PE and PE arms, respectively. The incidence of grade 3-4 AEs was similar between arms, but there was a higher (14.8% versus 6.2%) discontinuation rate in the pembrolizumab arm. The treatment-related death rate was 6.3% versus 5.4% for the pembrolizumab and PE arms, respectively.

Nivolumab (anti-PD-1) plus PE

ECOG-ACRIN EA5161 is a phase II study which randomised (1 : 1) 160 patients with ED-SCLC to four cycles of PE (carboplatin or cisplatin) plus nivolumab followed by nivolumab for 2 years (nivolumab-PE) or PE alone.[33] The primary endpoint was investigator-assessed PFS. The trial was designed to detect a 37.5% reduction in the PFS HR. Baseline characteristics were well balanced, but there was a higher (14% versus 9%) percentage of patients with brain metastases at baseline in the nivolumab-PE arm. PFS was significantly longer (5.5 versus 4.7 months, HR 0.68, 95% CI 0.48-1.00; $P = 0.047$) in the nivolumab-PE arm. In the intention to treat (ITT) group, HR for PFS was 0.65 (95% CI: 0.46-0.91; $P = 0.012$). In addition, OS (11.3 versus 8.5 months, HR 0.67, 95% CI 0.48-0.98; $P = 0.038$) and ORR (52% versus 47%) were also higher in the experimental arm. The incidences of grade 3-4 AEs and AEs leading to treatment discontinuation were 77% and 6.21% versus 62% and 2.07% for the nivolumab-PE and PE arms, respectively.

IMMUNE CHECKPOINT BLOCKADE AS MAINTENANCE TREATMENT

Early tumour relapse after the initial response to first-line ChT provides a rationale for maintenance therapy in ED-SCLC. In a phase II single-arm study, 45 patients with ED-SCLC who did not progress after four to six cycles of PE, received pembrolizumab 200 mg/kg 3 weekly for up to 2 years, starting within 8 weeks from the last dose of PE.[34] PD-L1 expression was evaluated in tumour and stromal tissue. The endpoint of mPFS improvement of 3 months was not met; PFS was 1.4 months (95% CI: 1.3-2.8). Interestingly, the 1-year PFS and 1-year OS rates were 13% and 37%, respectively, and four patients continued treatment beyond 18 cycles. PD-L1 expression in the stroma was higher than in tumour cells (TC) and predicted a better outcome (this topic is discussed in detail in Section 3). According to the authors, these results suggested that there was a subset of patients benefiting from pembrolizumab maintenance and that stromal PD-L1 expression could be a potential biomarker.

CheckMate 451 was a phase III trial which randomised 834 patients with ED-SCLC who had not progressed after four cycles of PE to receive maintenance nivolumab (1 mg/kg every 3 weeks) plus ipilimumab (3 mg/kg every 3 weeks) up to four cycles, followed by nivolumab (240 mg every 2 weeks) or nivolumab alone (240 mg every 2 weeks) or placebo until disease progression, unacceptable toxicity or a maximum of 2 years.[35] Maintenance therapy started 3-9 weeks from the last dose of ChT in those patients not receiving PCI and 3-11 weeks in patients receiving PCI. Patients were stratified according to PS, sex and PCI. The primary endpoint of OS in patients treated with ICI doublet versus placebo was not met. OS was 9.2 versus 9.6 months (HR 0.84, 95% CI 0.8-1.1; $P = 0.37$) for ICI doublet versus placebo, respectively. Rates of grade 3-4 AEs and treatment discontinuation due to toxicity in ICI doublet, nivolumab alone and placebo were 31% and 25% versus 4% and 4% versus 3% and $<1\%$, respectively. One potential reason for negative results is that almost 60% of the patients received maintenance after ≥ 5 weeks from the last ChT dose and the median number of cycles in the ICI doublet arm was only one as a consequence of severe toxicity. Furthermore, it is not possible to assess the statistical benefit of nivolumab versus placebo because this was not formally tested due to the hierarchy of the statistical design.

PREDICTIVE BIOMARKERS

At present, no predictive biomarkers for ORR or OS to ICI in ED-SCLC have been validated for use in clinical practice. The clinical utility of PD-L1 expression and TMB is still under investigation.

PD-L1

PDL-L1 expression in TC may potentially identify NSCLC patients who are more likely to benefit from ICI. However, PD-L1 interpretation can be difficult due to intratumoural heterogeneity, dynamic changes and different testing methods with different cut-off thresholds, which hinders cross-trial comparison and data validation.[36-38]

The frequency of PD-L1 expression in SCLC is discordant between series, but tends to be substantially lower compared with NSCLC.[17,19,39-43] Yasuda et al.[44] evaluated the expression of PD-L1 in 39 SCLC samples using the Dako 22C3 clone and cut-off of $\geq 1\%$ PD-L1 expression in TC. Only one patient was PD-L1-positive. In CHECKMATE-032,[17] a phase Ib/II trial evaluating nivolumab versus nivolumab/ipilimumab in recurrent ED-SCLC, 69% of the patients ($n = 148$) were assessable for PD-L1 expression in TC using the Dako clone 28-8 assay. Seventeen percent of the patients had a PD-L1 expression of $\geq 1\%$ and responses were observed irrespective of PD-L1 expression.

According to recent publications, PD-L1 expression in stroma cells could play an essential role in checkpoint blockade therapy and help predict clinical efficacy to programmed cell death protein 1 (PD-1)/PD-L1 in some solid cancers.[45,46] Schultheis et al.[42] measured PD-L1 expression with two different antibodies (5H1 and E1L3N) in 94 small-cell carcinoma samples (61 pulmonary). None of the samples tested for PD-L1 in TC was positive whereas 19% were positive in stroma cells. In KEYNOTE-028, a phase Ib multicohort trial with 24 recurrent ED-SCLC, 32% of the assessed patients had PD-L1 expression $\geq 1\%$.[47] In this study, PD-L1 positivity was defined as PD-L1 expression $\geq 1\%$ by 22C3 pharmDx assay in tumour and associated inflammatory cells or positive staining in stroma. Similarly, a pre-planned exploratory analysis in the KEYNOTE 158 sudy[19] found that 39% of the patients had PD-L1 $\geq$ 1%. ORR (39% versus 6%) and OS (14.6 versus 7.7 months) were higher in PD-L1-positive patients.

In the trial evaluating maintenance pembrolizumab following induction PE, a modified proportion score was used to assess PD-L1 expression in TC.[34] Mononuclear cells within TC nests staining for PD-L1 were counted in combination with TC positive for PD-L1. In addition, PD-L1 expression in the surrounding stroma was also assessed. Thirty (67%) patients were assessable for PDL1 expression in TC; only three (10%) patients were positive ($\geq 1\%$ PD-L1) and two of them achieved partial response. PD-L1 stroma expression was assessed in 20 patients; 8 (40%) of them were positive and achieved longer median PFS (6.8 versus 1.3 months) and OS (12.8 versus 7.6 months) compared with negative patients. However, this was a single-arm study with a limited sample and no definite conclusions can be drawn.

In IMpower133,[25] PD-L1 testing was not mandated at trial entry owing to an expected high rate of inadequate sample types (i.e. fine-needle aspirations), low prevalence of PD-L1 expression and a lack of association between response and PD-L1 expression in a previous phase II trial of atezolizumab versus ChT in recurrent ED-SCLC.[48] A *post hoc* exploratory analysis was conducted to evaluate the impact of PD-L1 expression on OS.[26] The PD-L1 assessable population represented 34% ($n = 137$) of the ITT population. PD-L1 status was assessed using the Ventana SP263 assay and efficacy analysis was conducted using PD-L1 expression cut-

offs of ≥1% and ≥5% in TC versus immune cells (IC). PD-L1 expression was higher in IC versus TC (cut-off 1%: 50.4% versus 1.8%; cut-off 5%: 20.4% versus 1.5%). There was no statistically significant difference in OS between the two arms according to the two prespecified PD-L1 expression cut-offs. HR for OS in PD-L1 < 1% versus ≥1% and <5% versus ≥5% in IC or TC was 0.51 (0.30-0.89) versus 0.87 (0.51-1.49) and 0.77 (0.51-1.17) versus 0.60 (0.25-1.46), respectively. No differences were found according to PD-L1 expression.

In CASPIAN,[29] 277 (52%) patients across the PE and durvalumab-PE arms had sufficient tissue to assess PD-L1 expression on TC and IC (SP263 assay). Approximately 95% and 78% of patients had PD-L1 expression <1% on TC and IC, respectively. OS benefit with durvalumab-PE was seen regardless of PD-L1 expression using a cut-off of 1% in TC or IC. HR for OS in PD-L1 < 1% versus ≥1% in TC and PD-L1 < 1% versus ≥1% in IC was: 0.66 (0.49-0.89) versus 0.46 (0.12-1.79) and 0.64 (0.46-0.89) versus 0.69 (0.37-1.28). No significant interaction was observed with OS based on PD L1 expression as a continuous variable (TC, $P = 0.54$ and IC, $P = 0.23$); similar results were observed with PFS and ORR.

In KEYNOTE-604, a tumour biopsy for PD-L1 assessment was mandatory. PD-L1 expression was assessed using the 22C3 pharmDx clone and measured using the combined positive score defined as the number of PD-L1-staining cells (TC, lymphocytes, macrophages) divided by the total number of viable TC, multiplied by 100. A total of 97 (43.1%) patients in the pembrolizumab-PE arm and 88 (38.6%) in the PE arm were PD-L1 ≥ 1%. In subgroup analyses, PFS and OS benefit was seen irrespectively of PD-L1 expression. HR for PFS and OS in PD-L1 ≥ 1 were 0.68 (0.49-0.94) and 0.84 (0.6-1.18), respectively.

TMB

TMB is an emerging biomarker independent of PD-L1 expression. In several tumour subtypes, high TMB tends to correlate with increased ORR to ICI.[49] SCLC exhibits a high mutational load due to tobacco-induced carcinogenesis. This leads to high non-synonymous somatic mutations resulting in neoantigens that can generate specific T-cell responses.

In CheckMate 032,[17] whole genome sequencing was used to quantify tumour somatic mutational load in tissue and paired whole blood samples. A total of 211 (53%) patients had sufficient tissue for TMB (133 patients in the nivolumab arm and 78 in the nivolumab/ipilimumab arm). TMB results were allocated in three groups according to the total number of non-synonymous somatic mutations per megabase (mut/Mb); low (0-142 mut/Mb), medium (143-247 mut/Mb) and high (≥248 mut/Mb). ORR was higher in TMB-high patients compared with TMB-medium/low both in the nivolumab and nivolumab plus ipilimumab arms. One-year PFS and 1-year OS were higher in the TMB-high population compared with medium/low TMB patients treated with nivolumab/ipilimumab (30% versus 8/6% and 62% versus 20/23%, respectively), but no differences were seen in the nivolumab alone arm. These results indicate that TMB could be potentially used to select ED-SCLC patients for ICI doublet, but further validation is required.

Blood-based TMB (bTMB) is an attractive alternative to tumour-based TMB due to scanty tissue usually obtained in diagnostic samples. However, the correlation between tumour and blood TMB is not known and results are not interchangeable. In IMpower133, an exploratory analysis of bTMB was conducted using two prespecified cut-offs of 10 mut/Mb and 16 mut/Mb. This did not show any difference in OS: HR in <10 versus ≥10 mut/Mb and <16 versus ≥16 mut/Mb were 0.73 (0.49-1.08) versus 0.73 (0.53-1.0) and 0.79 (0.60-1.04) versus 0.58 (0.34-0.99), respectively. An exploratory analysis of the CASPIAN trial investigated the association of tumour TMB (tTMB) with efficacy outcome. tTMB was assessed using FoundationOne CDX platform, and 283 patients (35% of the ITT population) were assessable. tTMB was not predictive of OS improvement for doublet ICI-PE versus PE measured as a continuous variable or using different cut-offs (<8 versus ≥8, <10 versus ≥10, <12 versus ≥12, <14 versus ≥14 mut/Mb).[50]

A recent retrospective study used targeted next generation sequencing (NGS) to measure TMB in a cohort of 52 patients with ED-SCLC treated with ICI.[51] Patients above the 50th percentile (TMB-high) had significantly longer median PFS (3.3 months versus 1.2 months, HR 0.37; $P < 0.01$) and OS (10.4 months versus 2.5 months, HR 0.38; $P < 0.01$), compared with patients below the 50th percentile (TMB-low). The authors concluded that targeted NGS may offer a cost-effective readily available diagnostic test to identify ED-SCLC patients who might benefit from ICI.

DISCUSSION AND FUTURE DIRECTIONS

The results from the IMpower133 and CASPIAN trials demonstrate that the addition of ICI to PE significantly improves OS in patients with untreated ED-SCLC, with a 25%-30% reduction in the risk of death. Noteworthy, survival benefit is sustained with 22% of patients alive at 2 years which represents a substantial improvement compared with historical data.[52]

Slight differences in trial design between IMpower133, CASPIAN and KEYNOTE-604 allow for some considerations. Firstly, the benefit of adding ICI to PE is observed regardless of the type of platinum salt used. The CASPIAN and KEYNOTE-604 trials allowed carboplatin or cisplatin as per investigator's choice whereas the IMpower133 trial only permitted carboplatin. In a prespecified subgroup analysis for OS in CASPIAN, no differences were observed between carboplatin and cisplatin, which is consistent with the subgroup analysis from KEYNOTE-604. Importantly, the type of platinum salt did not affect treatment delivery. These data are consistent with previous meta-analyses which failed to prove superiority of cisplatin over carboplatin in the first-line setting and seems to be also true for the ICI-PE combination.[53] The number of cycles of PE also differed between trials: IMpower133 and KEYNOTE-604 allowed up to four cycles whilst CASPIAN allowed up to six cycles in the

control arm. The median PFS of the control arm in CASPIAN was longer than in IMpower133 and KEYNOTE-604 (5.4 versus 4.3 months, respectively). This might be driven by the fact that half of these patients received six cycles. However, this increase in median PFS did not translate in better OS. In IMpower133 and KEYNOTE-604, patients could be treated with PCI in both arms and 10% of the patients in each arm received PCI. In contrast, CASPIAN only permitted PCI in the control arm (8%) but no difference in the incidence of brain metastases was observed between arms.[29] A small number of patients (9%-15%) with treated/asymptomatic brain metastases were included in these randomised trials. PFS and OS did not favour either arm.

The unexpected lack of OS benefit seen in KEYNOTE-604 is somewhat difficult to explain, but several factors might have contributed. The median OS of pembrolizumab-PE was 2 months shorter than that reported for atezolizumab and durvalumab. The authors suggest that KEYNOTE-604 might have enrolled sicker patients: more PS 1 patients (73% versus 63%), large tumour dimensions (134 versus 113 mm in IMpower133), higher percentage of patients with brain metastases (15% versus 9%-10%), higher lactate dehydrogenase and more patients with three or more metastases at baseline. Additionally, it is possible that median OS is not sufficient to capture ICI benefit: the survival curves for pembrolizumab and placebo initially overlap (resulting in similar median OS) and diverge at 5-6 months in favour of pembrolizumab. This separation is maintained over time resulting in a 2-year OS of 22% in pembrolizumab versus 11% in placebo consistent with prior observations from the IMpower133 and CASPIAN trials. KEYNOTE-604 is considered a positive trial as the co-primary endpoint of PFS was met; however, it is unlikely that this will impact in clinical practice. In this context, the EA5161 study also showed significantly longer PFS and OS with nivolumab-PE. Notably, this was a small phase II study not powered to detect OS difference but, in the current scenario, a phase III trial to confirm OS activity is not expected.

Irrespective of the regulatory approval of pembrolizumab and nivolumab in this setting, the KEYNOTE-604 and EA5161 trials support the activity of PD-1/PD-L1 inhibition for the treatment of ED-SCLC. Conversely, CTLA-4 inhibitors have failed to prolong PFS or OS in several trials with ipilimumab-ChT,[22-24] and, more recently, with tremelimumab plus durvalumab-PE.[30] Moreover, the addition of tremelimumab translated into a higher incidence of grade 3-4 AEs (70% and 62.3% in doublet ICI versus durvalumab, respectively) and doubled the treatment discontinuation rate and treatment-related deaths (21% versus 10.2% and 12 versus 6 patients, in doublet ICI and durvalumab, respectively). In our opinion, CTLA-4 inhibition is not a useful strategy in ED-SCLC and its use could only be justified in the presence of predictive biomarkers.

The four randomised studies with PD-1/PDL-1 inhibitors plus PE[25,28,32,33] demonstrate that ICI induce long-term survival in SCLC in line with prior data from NSCLC and other malignancies. The fact that the survival curve seems to reach a plateau highlights the relevance of tumour heterogeneity, but also the need for a predictive biomarker to select patients for ICI benefit. In this context, the clinical utility of TMB is controversial. CheckMate 032 suggested its potential to predict the benefit of doublet ICI in recurrent ED-SCLC. By contrast, allowing for differences between blood and tumour-based TMB, IMpower133 failed to demonstrate a difference in OS according to bTMB levels. Moreover, TMB evaluation requires complex and expensive techniques not available to most clinicians. Future studies should aim to validate testing techniques and cut-offs, while considering the feasibility to implement these techniques in daily practice.

In SCLC, PD-L1 expression in immune/stroma cells is higher compared with TC, but its clinical significance is uncertain. The KEYNOTE-158 and NCT02359019 trials showed a positive correlation between stroma PD-L1 positivity and response to ICI but this was not confirmed in the CASPIAN, IMpower133 and KEYNOTE-604 trials. Many factors might have contributed to these discrepancies between trials such as the use of different assays and methods (combined scored of tumour/stroma versus IC), and also how ICI is delivered (ICI alone or in combination with ChT). In our opinion, it is unlikely that PD-L1 is of value in clinical practice. Thus, a deeper understanding of tumour biology is required to identify and refine biomarkers. In this context, Rudin et al.[54] proposed a classification of SCLC in four subtypes defined by the differential expression of four key transcription regulators (ASCL1, NeuroD1, YAP1 and POU). The therapeutic and clinical implication of this classification is under investigation. A recent abstract presented in ASCO 2020 highlighted that YAP1 subtype had a longer OS and was enriched for T-cell inflamed phenotype, which in turn could predict for a clinical benefit of immunotherapy.[55]

In the next few years, several upcoming trials evaluating the combination of PE plus different PD-1/PD-L1 inhibitors will report results adding valuable clinical data and further understanding on tumour biology (Table 2).

REACTION is a phase II trial led by the European Organisation of Research and Treatment of Cancer (EORTC) which enrols patients with ED-SCLC who have achieved either partial or complete response after two cycles of carboplatin and etoposide. Patients will then be randomised to continue carboplatin and etoposide for a further four cycles or to receive four cycles of carboplatin and etoposide plus pembrolizumab followed by pembrolizumab maintenance until progression. Interestingly, patients in the control arm are allowed to cross over to pembrolizumab-PE if progressive disease occurs at least 3 months after PE completion.

Consolidation thoracic radiotherapy in ED-SCLC can improve survival in patients with good extrathoracic disease control after first-line ChT.[6] However, this strategy is not extensively adopted and due to the potential increased risk of pneumonitis, was not permitted in ICI-PE pivotal trials (IMpower133, CASPIAN, KEYNOTE-604 and EA5161). Radiotherapy can enhance ICI activity by increasing antigen presentation, neoantigen formation and microenvironment modification.[56] The NCT02934503 trial will evaluate the

Table 2. Ongoing trials plus immune checkpoint inhibitors in first-line setting and/or maintenance for extensive stage small-cell lung cancer

Combination	Trial ID	Agent	Phase	*N*	Study design	Treatment	Endpoint	Status	Completion date
ICI + ChT	NCT02580994 (REACTION)	Pembrolizumab	II	118	Randomised, open-label, crossover of PE with/out pembrolizumab in patients with PR/CR after 2C of PE.	Arm A: PE + pembrolizumab × 4C → pembrolizumab Arm B: PE × 4C	PFS	Recruiting	Aug 2020
	NCT03568097 (PAVE)	Avelumab	II	55	Open-label, single-arm study of phased avelumab plus PE	Arm A: PE + phased avelumab	1 year PFS	Recruiting	Aug 2021
	NCT04063163	HLX10 (PD-1 inhibitor)	III	489	Randomised, double-blind, study of PE with/out HLX10	Arm A: HLX10 + PE Arm B: placebo + PE	PFS	Recruiting	Dec 2021
	NCT03711305	SHR-1316 (PDL-1 inhibitor)	III	396	Randomised, double-blind of PE with/out SHR-1316	Arm A: SHR-1316 + PE × 4-6C → SHR-1316 Arm B: placebo + PE → placebo	PFS and OS	Not yet recruiting	Dec 2022
	NCT04012606	Toripalimab (PDL-1 inhibitor)	III	420	Randomised, Double-blind of toripalimab with/out PE	Arm A: PE + toripalimab → toripalimab Arm B: PE + placebo → placebo	PFS and OS	Recruiting	June 2022
	NCT04005716	Tislelizumab (PD-1 inhibitor)	III	364	Randomised, double-blind of PE with/out tislelizumab	Arm A: tislelizumab + PE × 4C → tislelizumab Control arm: placebo + PE × 4C → placebo	PFS and OS	Recruiting	June 2022
	NCT04221529	Atezolizumab	II	70	Open-label, single-arm study of PE plus atezolizumab in PS 2 patients	Arm A: PE + atezolizumab → atezolizumab	OS	Recruiting	June 2024
ICI doublet + ChT	NCT03963414	Durvalumab + tremelimumab	I	18	Open-label study of PE + durvalumab with/out tremelimumab in PS 2 patients	Arm A: durvalumab + tremelimumab + PE → durvalumab Arm B: durvalumab + PE → durvalumab	Treatment-related adverse event > grade 3	Not yet recruiting	July 2022
ICI + ChT + other agent	NCT03041311	Atezolizumab and Trilaciclib	II	105	Randomised study of PE and atezolizumab with/out trilaciclib	Arm A: PE plus atezolizumab + trilaciclib → atezolizumab Control arm: PE plus atezolizumab + placebo → atezolizumab	Evaluate the potential of trilaciclib to reduce chemotherapy-induced myelosuppression	Active, not recruiting	May 2020
	NCT04256421 (SKYSCRAPER-02)	Atezolizumab and tiragolumab (TIGIT inhibitor)	III	400	Randomised, double-blind study of atezolizumab plus PE with/out tiragolumab	Arm A: PE + atezolizumab plus trilaciclib → atezolizumab Control arm: PE + atezolizumab + placebo → atezolizumab	PFS, OS	Recruiting	August 2023
	NCT04101357	Atezolizumab and BNT411 (TLR7 agonist)	I/II	60	Open-label, single-arm study of BNT411 plus atezolizumab plus PE (part 1B)	Arm A: PE + atezolizumab + BNT411	DLT, AEs, dose reduction and discontinuation due to AEs	Not yet recruiting	Dec 2023
	NCT02934503	Pembrolizumab and RT	II	60	Open-label, single-group. of pembrolizumab and dynamic PD-L1 expression	Arm A: PE + pembrolizumab → pembrolizumab and RT Cohort B: PE + pembrolizumab → pembrolizumab Cohort C: PE → pembrolizumab Cohort D: PE + RT → pembrolizumab	Change in PD-L1 expression status	Recruiting	Oct 2020
Maintenance	NCT03319940	AMG 757 (BiTE targeting DLL3) ± pembrolizumab	I	162	Open-label study of AMG757 monotherapy or in combination with pembrolizumab in first-line/ recurrent SCLC	Part A and C: AMG757 + pembrolizumab in recurrent SCLC Part B: AMG757 in patients with ongoing benefit after 6C of platinum ChT	DLTs	Recruiting	Aug 2023

Continued

Table 2. Continued

Combination	Trial ID	Agent	Phase	N	Study design	Treatment	Endpoint	Status	Completion date
	NCT03410368	NK Cell-based immunotherapy	II	120	A randomised, open-label study of NK cell-based immunotherapy as maintenance therapy after SD/PR/CR to PE	Arm A: three consecutive infusions of NK cells for a total of six courses	PFS	Recruiting	July 2020
	NCT03958045	Nivolumab + ricaparib	II	36	Open-label, single-group study of rucaparib plus nivolumab as maintenance therapy after PR/CR with PE	Arm A: nivolumab + ricaparib	PFS	Recruiting	July 2024

AEs, adverse cvent(s); BiTE, bispecific T cell engager; C, cycles; ChT, chemotherapy; CR, complete response; DLT, dose-limiting toxicity; DLL3, Delta-like protein 3; ICI, immune checkpoint inhibitor; NK, natural killer; OS, overall survival; PD-1/PDL-1, programmed death 1/programmed death-ligand 1; PE, platinum and etoposide; PFS, progression-free survival; PR, partial response; PS, performance status; RT, radiotherapy; SCLC, small-cell lung cancer; SD, stable disease; TIGIT, T-cell immunoreceptors with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains.

dynamic changes in PD-L1 expression, in patients with ED-SCLC treated with ICI-PE with or without chest radiotherapy. This trial will help to understand the biological and clinical impact of chest radiotherapy in this setting.

Patients with newly diagnosed ED-SCLC often present with borderline/poor PS due to symptoms secondary to large and rapidly growing tumour masses. While treatment of PS 3-4 patients is controversial, standard PE is indicated in PS 2, since high response rate allows rapid PS improvement.[6] However, ICI-PE pivotal trials excluded PS 2 patients extrapolating indications for NSCLC. Two ongoing trials dedicated to the PS 2 population (NCT04221529 and NCT03963414) will try to cover this area of unmet need. NCT04221529 is a small, single-arm, phase II study to evaluate PE plus atezolizumab in patients with PS 2. The primary endpoint is OS. NCT03963414 is a phase I trial to evaluate the combination of PE with durvalumab with or without tremelimumab in patients with PS 2. The primary endpoint is treatment-related AEs grade 3 or higher.

Several ongoing trials are investigating the addition of novel drugs with the potential to promote tumour immunity in combination with a backbone of PE plus ICI. In this setting, a promising drug is trilaciclib, an intravenous CDK4/6 inhibitor that preserves hematopoietic stem and progenitor cells leading to faster hematopoietic recovery and enhanced antitumour immunity. A phase Ib/II[57] trial evaluated the safety, efficacy and pharmacokinetics of trilaciclib in combination with PE in patients with ED-SCLC. A total of 122 patients were enrolled; 19 patients were included in part 1 (open-label, dose finding) and 75 patients in part 2 (randomised, double-blind, placebo-controlled). Improvements were seen with trilaciclib in neutrophil, red blood cell and lymphocyte measures. Safety on trilaciclib-PE was improved with fewer G3 AEs compared with placebo-PE (50% versus 83.8%), primarily due to less haematological toxicity. No trilaciclib-related G3 AEs occurred. Antitumour efficacy did not differ between trilaciclib-PE and placebo-PE, ORR of 66.7% versus 56.8% ($P = 0.3831$), PFS 6.2 versus 5.0 months (HR 0.71, 95% CI 0.51-0.98; $P = 0.1695$) and OS of 10.9 versus 10.6 months (HR 0.87, CI 95% 0.61-1.24; $P = 0.6107$). These data support the myelopreservation benefits of trilaciclib with no detriment in antitumour activity. NCT03041311 is a randomised phase II trial to evaluate the potential of trilaciclib to reduce ChT-induced myelosuppression in treatment-naive ED-SCLC patients treated with atezolizumab/PE with or without trilaciclib. Results from this trial are expected for 2020.

Tiragolumab is a human monoclonal antibody targeting T-cell immunoreceptors with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT). TIGIT is a member of the immunoglobulin superfamily expressed on the surface of activated T cells and natural killer (NK) cells. TIGIT interacts with high affinity with CD155, also known as the poliovirus receptor (PVR). The activation of TIGIT limits antitumour immune responses via reduction of tumour-associated lymphocytes efficacy, T cells and NK cells proliferation, cytokine production and killing of target TC. Notably, high expression levels of PD-L1 and

CD155 (TIGIT receptor) were independent prognostic factors for poor survival in a cohort of 60 patients with resected SCLCs.[58] Because TIGIT and PD-1 are coordinately expressed by infiltrating T cells in several human tumours, inhibition of the TIGIT/PVR axis might potentiate the antitumour activity of PD-1/PD-L1 inhibitors.[59,60] In preclinical models, concomitant blockade of TIGIT/PVR and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent treatments. Additionally, the primary analyses of CITYSCAPE,[61] a phase II study in metastatic NSCLC evaluating atezolizumab with tiragolumab or placebo, demonstrated higher PFS and ORR in the tiragolumab arm; 5.6 months and 37.3% versus 3.9 months and 20.6%, respectively. A large phase III trial (SKYSCRAPER-02) will evaluate atezolizumab plus PE with tiragolumab or placebo in ED-SCLC. The co-primary endpoints are PFS and OS.

Another novel compound designed to stimulate cancer immunity is BNT411, a TLR7 agonist designed to activate both the adaptive and innate immune system through the TLR7 pathway. This activity and the release of cytokines and chemokines are designed to result in the potent stimulation of antigen-specific CD8+ T cells, B cells and innate IC such as NK cells and macrophages. NCT04101357 is a phase I/II study to evaluate BNT411 in monotherapy in several solid tumours and will include a dedicated cohort (part 1B) for treatment-naive ED-SCLC which will receive BNT411 in combination with PE and atezolizumab.

AMG 119 is an adoptive cellular therapy that consists of a patient's autologous T cells that have been genetically modified *ex vivo* to express a transmembrane chimeric antigen receptor (CAR) that targets Delta-like ligand 3 (DLL3) and redirects cytotoxic T cell specificity to DLL3-positive cells. AMG 119 CAR T cells show potent killing of SCLC cells expressing DLL3 *in vitro* and inhibit tumour growth in an SCLC xenograft model *in vivo*. NCT03392064 is a phase I study evaluating the safety, tolerability and efficacy of AMG 119 in subjects with relapsed/refractory SCLCs.

The epigenetic machinery plays an important role in cancer processes, especially in SCLC, and is a promising anticancer target. Recent research shows that two epigenetic regulatory proteins, enhancer of zeste homology 2 (EZH2) and lysine-specific demethylase 1A (LSD1), could augment the response of ICI in SCLC, both of which will be investigated in upcoming clinical trials.[62]

Thus far, ICI given as maintenance therapy have not improved outcomes in ED-SCLC. The four randomised trials of PD-1/PD-L1 plus PE show that PFS curves diverge in favour of ICI at 4-6 months (after ChT completion) which might indicate that maintenance ICI could be driving PFS benefits. However, the two maintenance trials with ICI monotherapy or doublet therapy (NCT02359019/CheckMate-451) failed to prolong PFS or OS. As previously discussed, many factors could be responsible for the lack of clinical impact and, in CheckMate-451, the efficacy of nivolumab alone was not formally tested. In this context, it is also possible that ICI alone are not enough to overcome the aggressive biology of SCLC and need to be combined with other therapies to attain a significant impact. Ongoing trials will continue to explore new maintenance strategies.

DLL3 is an inhibitory ligand of Notch receptors that is expressed in most SCLC tumours, but minimally expressed in normal tissues. DLL3 represents a promising target for T-cell redirecting immunotherapy. AMG 757 is a half-life extended bispecific T cell engager (BiTE) antibody construct that is designed to transiently connect DLL3-positive cells to CD3-positive T cells and induce T cell-mediated cell lysis and concomitant T cell proliferation. NCT03319940 is a phase I study evaluating AMG 757 monotherapy with or without pembrolizumab as consolidation therapy, or after failure with platinum ChT. The trial has a dose exploration phase to determine the primary endpoint of maximum tolerated dose and a dose expansion phase for clinical efficacy. Patients with recurrent/progressive disease after platinum-based ChT will be allocated to AMG 757 alone (cohort A) or in combination with pembrolizumab (cohort C). The maintenance arm (cohort B) with AMG 757 alone will include patients with clinical benefit (stable disease, partial response or complete response) following first-line platinum-based ChT.

NCT03410368 is a phase II randomised trial in which patients not progressing after four cycles of PE will be randomised to standard follow-up or autologous NK cells expanded *ex vivo* aiming to promote an innate immune system and kill tumour cells in a non-MHC-restricted manner. The primary endpoint of this study is PFS.

In another trial (NCT03958045), patients will receive maintenance therapy with rucaparib plus nivolumab until disease progression. This trial is based on the preclinical data published by Byers et al.[63] showing that the combination of the poly ADP-ribose polymerase (PARP) inhibitor olaparib or the checkpoint kinase 1 inhibitor prexasertib, together with ICI, significantly increased the effect of PD-L1 blockade, augmented cytotoxic T-cell infiltration and activated innate immune pathways leading to rapid tumour regression in *in vivo* mouse models. In addition, SLFN11 was described as a potential biomarker to predict benefits from PARP inhibitors opening the door for precision medicine in SCLC.

In conclusion, the addition of anti-PD-L1 inhibitors atezolizumab or durvalumab to first-line PE represents an important therapeutic advance for ED-SCLC patients. This new strategy opens new challenges such as the identification and validation of tumour biomarkers for patients' selection, overcoming chemo/immune-resistance and fine-tuning tumour immunity to improve outcomes.

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