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Hot Topic

The evolving landscape of immunotherapy in small-cell lung cancer: A focus on predictive biomarkers

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ABSTRACT

Small cell lung cancer (SCLC) was defined as a "recalcitrant cancer" because of its dismal prognosis and lack of outcome improvements in the last 30 years. Immunotherapy with checkpoint inhibitors revolutionized treatment in many cancer types and results from the IMpower133 study, a double-blind placebo-controlled phase III trial, showed overall survival benefit for atezolizumab when added to standard platinum-etoposide chemotherapy in first-line SCLC setting for the first time since years. Trials with other checkpoint inhibitors, e.g. pembrolizumab, durvalumab, nivolumab and ipilimumab, are ongoing in various settings, but, to date, there are no defined factors to identify patients who are more likely to benefit from such treatments. This review summarizes results of immunotherapy trials in SCLC for first-line, maintenance and further-line therapies for single-agents and combinations with checkpoint inhibitors. Predictive factors from these trials are reviewed in order to identify their clinical value, with particular emphasis on PD-L1 expression on both tumor cells and in stroma, especially in pembrolizumab-treated patients, and tumor mutational burden, for patients treated with the ipilimumab and nivolumab combination.

Introduction

Small Cell Lung Cancer (SCLC) accounts for 15–17% of all lung cancers. Most patients have metastatic disease at the time of diagnosis, with a 5-year survival rate of only 2–8%. In this context, unfortunately, no improvement in survival has been achieved in the last 30 years [1]. In first-line setting, the standard of care is still based on platinum-etoposide [2], with platinum-irinotecan being an alternative option in Japan [3]. Although high response rates to first-line chemotherapy are observed (around 70–80%), most patients relapse within few months, leading to a median overall survival (mOS) of 8–12 months [4]. At relapse, topotecan is the only approved drug, following data on its antitumor activity (response rates of 7–38%) and a significant improvement in survival when compared to best supportive care (mOS: 26 vs 14 weeks) [5,6]. Nowadays, amrubicin single agent regimen represents an alternative treatment for Japanese refractory patients, but its superiority over topotecan has not been demonstrated in Western population [7].

Given its dismal prognosis, SCLC has been defined as one of the "recalcitrant" cancers with the "Recalcitrant Cancer Research Act of 2012", with urgent need for therapeutic innovations [8].

Considering the lack of therapeutic options able to induce durable responses, the field of precision medicine is being deeply explored in order to assess a possible role of targeted therapy in SCLC. In particular, treatment strategies with antiangiogenic molecules, such as bevacizumab, sorafenib and vandetanib, failed to improve survival as first-line or maintenance treatment [9–12], as confirmed also by a recent meta-analysis [13]. Nevertheless, two recent trials on antiangiogenic drugs (apatinib and anlotinib), have shown promising activity in heavily pretreated patients, gaining attention in this research field [14,15]. Studies on tyrosine-kinase inhibitors, such as imatinib, erlotinib, gefitinib as well as mTOR inhibitors, have also led to daunting results [16].

The search for *druggable* genomic aberrations has shown that SCLC is characterized by a high number of genetic alterations, including the concomitant loss of *TP53* and *Retinoblastoma 1* (*RB1*) which is observed

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in up to 90% of the cases [17]. Other molecular alterations involve fibroblast growth factor receptor 1 (*FGFR1*), phosphoinositide 3-kinase (*PI3K*), phosphatase and tensin homolog (*PTEN*), mesenchymal epithelial transition kinase (*MET*), *MYC*, Mixed-Lineage Leukemia Protein 2 (*MLL2*), LDL Receptor Related Protein 1B (*LRP1B*), Sex Determining Region Y-Box 2 (*SOX2*) and Poly(ADP-Ribose) Polymerase 1 (*PARP1*) [18]. However, since most of them are believed to be *passenger* molecular aberrations, their inhibition does not affect significantly tumor cell survival. Nevertheless, the overflowing spreading of next generation sequencing (NGS) techniques, has contributed to the identification of new potentially targetable altered genes and signaling pathways, such as the NOTCH family genes and Schlafen-11 (SLFN11) [19]. NOTCH signaling pathway inhibits tumor development and is found to be inactivated in about 25% of SCLC [17]. DLL3 is a suppressor of NOTCH, which is expressed in about 80% of SCLC [20–22], and is the target of the first-in-class antibody-drug conjugate rovalpituzumab tesirine (Rova-T), under evaluation in SCLC. On the other hand, expression of SLFN11, a regulator of response to DNA damage and replicative stress, is correlated to response to PARP inhibitors and was associated to better outcomes in a phase II double-blind study with temozolomide and veliparib [23].

Immunotherapy in SCLC

SCLC is strongly linked to a potent carcinogen such as tobacco smoking [17] and has a high proliferation rate which makes tumor cells prone to the development of genomic aberrations, DNA damage and genomic instability. These conditions make SCLC cells dependent on the DNA damage repair (DDR) machinery and cell cycle checkpoints in order to continue proliferating. A better understanding of tumor immunology and recent clinical advances in cancer immunotherapy have opened new therapeutic perspectives, especially for tumors with limited treatment options. Cluster of Differentiation 8 positive (CD8 +) cells are the main effector against human tumors and their activation requires a double signal: the first one stimulates the T-cell receptor (TCR) and is mediated by antigen-presenting cells (APC) with processed antigens presented in association with major histocompatibility complex I (MHC I); the second one is based on the engagement of CD28 by B.7, acting as costimulator. The presence of negative costimulatory signals able to inhibit T cell activation is crucial in the regulatory machinery of T cell activation. The human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1) are the best characterized to date and are regarded to as immune checkpoints: their blockade can disrupt the negative feedback loop, restoring tumor-specific immunity against cancer cells. Since 2011, when the first immune checkpoint inhibitor (ICI) ipilimumab, a fully humanized IgG1 antibody against CTLA-4, was approved for clinical use in advanced melanoma, ICIs provided exciting results. Several observations suggested a possible role of immunotherapy in SCLC, as well. First, SCLC cells have a remarkably high number of somatic non-synonymous mutations (tumor mutational burden, TMB), reported to be between 7.4 and 8.62 mutations per million of bases [17,18,24]. These protein-changing mutations are associated to tobacco smoking exposure, as highlighted by the elevated rate of C:G > T:A transversions, and are able to determine a high neoantigens load. There is strong evidence that in solid tumors the number of antigenic mutations is a trigger for a greater tumor-specific T-cell response [25,26]. Second, SCLC is an immunogenic disease since 15–20% of newly diagnosed SCLC patients have clinical evidence of some paraneoplastic syndrome, such as Lambert-Eaton syndrome, sensory neuronopathy, encephalomyelitis or paraneoplastic cerebellar degenerations. This correlation is due to a cross-reactivity between cancer cells and different component of the nervous system, mediated by well-defined antibodies (anti-Hu, anti-Ma, anti-variable-gated calcium channel). Notably, the development of such immune-mediated paraneoplastic syndromes is associated with longer survival [27]. Furthermore, the presence of serum anti-neuronal nuclear antibodies, even in those patients who do not develop a clinical neurological syndrome, is associated with longer survival [28]. Third, SCLC induces an immune suppressive phenotype, through a relative increase of regulatory T-cells, compared to effector T-cells, in metastatic vs localized SCLC, and in recurrent SCLC [29]. The expression of mRNA encoding for immune suppressive molecules such as transforming growth factor beta (TGF-B), forkhead box P3 (FOXP3) and CTLA-4, is also higher in SCLC patients without paraneoplastic neurologic syndrome than in patients who have it [30]. The previous mentioned reasons provide the rationale for the use of ICIs in SCLC, in an attempt to enhance immune response. Clinical trials were carried out both in first-line setting and in relapsed SCLC to investigate single-agent ICIs, ICIs in combination with both chemotherapy or other ICIs [31–38] (Table 1).

Single agent immune checkpoint inhibition

Nivolumab is a human IgG4 monoclonal antibody targeting PD-1, preventing it from binding its ligand, programmed death ligand 1 (PD-L1). In SCLC, nivolumab was initially tested in the CheckMate-032 trial, a multi-cohort phase I/II study [31]. The aim of the study was to determine clinical activity of nivolumab monotherapy and safety, optimal dose and activity of the combination of nivolumab and ipilimumab at different dose combinations, irrespective of tumor PD-L1 expression. Primary endpoint was objective response rate (ORR) by RECIST criteria v1.1, while secondary endpoints were progression-free survival (PFS), overall survival (OS), duration of response (DOR) and adverse events leading to treatment discontinuation. At the time of the first data report from this multi-arm trial, 98 progressive SCLC patients were randomized to receive single-agent nivolumab at 3 mg/kg every two weeks. An ORR of 10% (95% CI 5–18%) was observed, while PFS and OS were 1.4 (95% CI 1.4–1.9) and 4.4 months (95% CI 3.0–9.3), respectively. The updated analysis in the expansion cohort confirmed an ORR of 11% leading to a 2-year OS rate of 17% [39]. A recent subgroup analysis of 109 patients receiving nivolumab monotherapy as third-line therapy reported an ORR of 11.9% (95% CI 6.5–19.5%), a median DOR of 17.9 months (range 3.0 to 42.1) and a 12-month OS rate (OS12) of 28.3% (95% CI 20.0–37.2%) [40]. Although these results are similar to those observed with third-line chemotherapy [41], it is interesting that nivolumab yielded a tail in DOR of up to 42 months in this analysis, even if restricted to a minority of patients. Furthermore, nivolumab monotherapy was well tolerated, with its known manageable toxicity profile. This data eventually led to Food & Drug Administration (FDA) granting accelerated approval to nivolumab monotherapy 240 mg flat dose every 3 weeks in metastatic SCLC patients progressing to first-line platinum-based chemotherapy and at least one other line of treatment [42].

The CheckMate-331 is a phase III trial which randomized (1:1 ratio) 569 SCLC patients who relapsed following platinum-based chemotherapy to receive nivolumab (284 patients) or standard second-line chemotherapy (topotecan or amrubicin, 285 patients). Results from this study were recently reported [43]. Primary endpoint of the study was OS. After a median follow-up of 7.0–7.6 months, Nivolumab did not improve OS compared with chemotherapy (mOS 7.5 [95% CI 5.6–9.2] vs 8.4 months [95% CI 7.0–10.0], p = 0.11). However, survival curves cross beyond about 11 months with sustained separation in favor of nivolumab, as highlighted by the progressive reduction in HR (from 1.46 to 0.49) when considering subsequent segments of the survival curves. This apparent delayed advantage of nivolumab over chemotherapy may reflect excess of early disease progressions and deaths in the nivolumab arm, as well as benefit from nivolumab in a subset of patients who also account for the longer median DOR in nivolumab (8.3 months, 95% CI 7.0–12.6) than in chemotherapy arm (4.5 months, 95% CI 4.1–5.8). Is it possible that recognizing this subset of patients could improve their outcome and let assign to chemotherapy those who are unlikely to respond to immunotherapy. In this direction, it is interesting to note that in an exploratory analysis nivolumab improved

Table 1
Clinical trials of immunotherapy agents in pretreated SCLC patients.

Study	CheckMate-032 [31]	CheckMate-032 [31]	KEYNOTE-028 [32]	KEYNOTE-158 [33]	Durvalumab [34]	Baltic Study [35]	IFCT-1603 [38]	CheckMate 451 [44]	CheckMate 451 [44]
Phase	II	I/II	I	II	I/II	II	II	III	III
Experimental arm	Nivo 3 mg/kg q2w	Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4 → Nivo 3 mg/kg q2w	Pembro 10 mg/kg q2w x 2 years	Pembro 200 mg q3w x 2 years	Durva 10 mg/kg q2w x 12 months	Durva 1500mg + Treme 75 mg q4w x 4 → Durva 1500 mg q4w	Atezo 1200 mg q3w	Nivo1/Ipi3 mg/kg q3w x 4 → Nivo 240 mg q2w x 2 years	Nivo 240 mg q2w x 2 years
Selection criteria	Biopsy/Tissue available for biomarkers	Biopsy/Tissue available for biomarkers	PD-L1 CPS ≥1%	Available tissue for PD-L1 determination	ED-SCLC PS 0-1	Pt-refractory	PS 0-2	ED-SCLC Maintenance setting PS 0-1	ED-SCLC Maintenance setting PS 0-1
Primary Endpoint	ORR	ORR	Safety ORR	ORR	Safety	ORR	ORR	OS (vs placebo)	OS (vs placebo)
No.	98	61	24	107	21	25	49	279	280
ORR, % (95%CI)	11%	25%	33% (16–55)	18.7% (11.8–27.4)	9.5%	9.5% (1.17–30.38)	2.3% (0.0–6.8)	45%	47%
mOS, months (95%CI)	4.1	7.9	9.7 (4.1–NR)	9.1 (5.7–14.6)	4.8 (1.3–10-4)	6.0 (1.9–12.0)	9.5 (3.2–14.4)	9.2 8.2–10.2)	10.4 (9.5–12.1)
OS12, % (95%CI)	30%	42%	37.7% (18.4–57.0)	34%	27.6% (10.2–48.4)	NA	42.5% (26.9–58.2)	41%	44%
mPFS, months (95%CI)	1.4 (1.4–1.9)	2.6 (1.4–4.1)	1.9 (1.7–5.9)	2.0 (1.9–2.1)	1.5 (0.9–1.8)	1.9 (1.8–4.3)	1.4 (1.2–1.5)	1.7 (1.5–2.6)	1.9 (1.6–2.6)
PFS12, % (95%CI)	11% (5–19)	19% (9–32)	23.8% (9.1–42.3)	16.9%	NA	NA	NA	NA	NA
G ≥ 3 AEs	14%	33%	8.3%	59%	0%	48%	4.2%	52%	12%
Predictive biomarker	TMB (ORR, mPFS, mOS) Pt sensitivity, PD-L1	TMB (ORR, mPFS, mOS)	NA	PD-L1 CPS ≥1% (ORR, mPFS, mOS)	NA	NA	PD-L1 on tumor and immune cells	NA	NA

ED-SCLC: extensive disease small cell lung cancer; LD-SCLC: limited disease small cell lung cancer; Nivo: Nivolumab; Ipi: Ipilimumab; Pembro: Pembrolizumab; Durva: Durvalumab; Treme: Tremelimumab; Atezo: Atezolizumab; Pt: Platinum; PD-L1: programmed death ligand 1; ORR: objective response rate; NA: not available; NR: not reached; mOS: median overall survival; OS12: 12-month overall survival rate; mPFS: median progression-free survival; PFS12: 12-month progression-free survival rate; 95%CI: 95% confidence interval; G ≥ 3 AEs: adverse events highest grade equal to or higher than 3.

Table 2
Immune checkpoint inhibitors trials in small cell lung cancer (source: clinicaltrials.gov – last accessed: 28th July 2019).

Study ID	Phase	Arms
Pembrolizumab		
First-line and/or maintenance treatment		
NCT01840579 (KEYNOTE-011)	I	CDDP/CBDCA + Etoposide + Pembrolizumab
NCT02402920	I	CDDP/CBDCA + Etoposide + Pembrolizumab + RT (LD-SCLC). CDDP/CBDCA + Etoposide + Pembrolizumab → RT + Pembrolizumab (ED-SCLC)
NCT02580994 (REACTION)	II	CDDP/CBDCA + Etoposide ± Pembrolizumab
NCT02934503	II	CDDP/CBDCA + Etoposide + Pembrolizumab → RT and Pembrolizumab (for up to 2 years) CDDP/CBDCA + Etoposide + Pembrolizumab (after the 1st cycle). CDDP + Etoposide → Pembrolizumab. Chemoradiotherapy → Pembrolizumab
NCT03066778 (KEYNOTE-604)	III	CDDP/CBDCA + Etoposide + Pembrolizumab/Placebo → Pembrolizumab/placebo (up to 2 years)
Second-line or further treatments		
NCT02646748	Ib	Pembrolizumab + Itacitinib (JAK1 inhibitor) Pembrolizumab + INCB050465 (PI3K inhibitor)
NCT02331251 (PembroPlus)	Ib/II	Pembrolizumab + Irinotecan
NCT02551432	II	Paclitaxel → Paclitaxel + Pembrolizumab → Pembrolizumab
NCT02963090	II	Pembrolizumab vs Topotecan
NCT03253068	II	Pembrolizumab + Amrubicin
NCT02628067 (KEYNOTE-158)	II	Pembrolizumab
NCT03371979 (Co-ArgI-PEG)	I/II	Pembrolizumab + Pegzilarginase (enhanced human arginase)
NCT03361228	I/II	INCB001158 (arginase inhibitor) + Epacadostat (IDO1 inhibitor) ± Pembrolizumab
NCT03277352	I/II	INCAGN01876 (anti-GITR agonistic monoclonal antibody) + Epacadostat (IDO1 inhibitor) ± Pembrolizumab
NCT03761914	I/II	Galinpepimut-S (WT1 Analog Peptide Vaccine) + Pembrolizumab
Nivolumab		
First-line and/or maintenance treatment		
NCT03043599	I/II	Nivolumab + Ipilimumab + consolidative RT
NCT02046733 (STIMULI)	II	Nivolumab + Ipilimumab (induction) for 4 cycles → Nivolumab (maintenance)
NCT03382561	II	CBDCA/CDDP + Etoposide ± Nivolumab → Nivolumab
NCT03958045	II	Nivolumab + Rucaparib (PARP inhibitor) (maintenance after objective response on CBDCA/CDDP + Etoposide)
Second-line or further treatments		
NCT02481830 (CheckMate-331)	III	Nivolumab vs Amrubicin/Topotecan
NCT03670056	II	Nivolumab + Ipilimumab (induction) for 4 cycles → Nivolumab (maintenance)
NCT03728361	II	Nivolumab + Temozolomide
NCT03026166	I/II	Rova-T + Nivolumab ± Ipilimumab (1 mg/kg or 3 mg/kg)
NCT02247349	I/II	BMS-986012 (anti-fucosyl-GM1) ± Nivolumab
NCT03325816	I/II	Nivolumab + 177Lu-DOTA0-Tyr3-Octreotate
NCT03406715	II	Nivolumab + Ipilimumab + Ad.p53-DC (Dendritic Cell based p53 Vaccine)
NCT03575793	I/II	Nivolumab + Plinabulin (tubulin inhibitor) ± Ipilimumab
NCT03662074	II	Nivolumab + Gemcitabine
NCT02922764	I	RGX-104 (LXR agonist) ± Nivolumab
NCT02712905	I/II	INCB059872 (LSD1 inhibitor) ± Nivolumab
NCT03126110	I/II	INCAGN01876 (anti-GITR agonistic monoclonal antibody) ± Nivolumab ± Ipilimumab
NCT03241173	I/II	INCAGN01949 (OX40 agonist) ± Nivolumab ± Ipilimumab
Atezolizumab		
First-line treatment and/or maintenance		
NCT03041311	II	CBDCA + Etoposide + Atezolizumab ± Trilaciclib (CDK4/6 inhibitor)
NCT03540420 (ACHILES)	II	Atezolizumab maintenance vs observation
Second-line or further treatments		
NCT03059667	II	Topotecan/CBDCA + Etoposide vs Atezolizumab
NCT03262454	II	Atezolizumab + Hypofractionated RT

(*continued on next page*)

Table 2 (*continued*)

Study ID	Phase	Arms
Avelumab		
First-line treatment and/or maintenance		
NCT03568097 (PAVE)	II	CBDCA/CDDP + Etoposide + Avelumab → Avelumab
Second-line or further treatments		
NCT02554812 (JAVELIN Medley)	II	Avelumab + Utomilumab (Anti-4-1BB antibody)
Durvalumab		
First-line treatment and/or maintenance		
NCT03703297 (ADRIATIC)	III	Durvalumab + Tremelimumab/Placebo Placebo (maintenance after concurrent chemo-radiation therapy)
NCT03585998	II	CDDP + Etoposide + Thoracic RT → Durvalumab
NCT03509012 (CLOVER)	I	Durvalumab ± Tremelimumab + CDDP + Etoposide + RT Durvalumab ± Tremelimumab + CDDP + Etoposide + Hypofractionated RT
NCT03923270	I	Thoracic RT → Durvalumab Thoracic RT → Durvalumab + Tremelimumab Thoracic RT → Durvalumab + Olaparib (PARP inhibitor)
NCT03963414	I	Durvalumab ± Tremelimumab + CBDCA + Etoposide in PS 2 patients

CDDP: Cisplatin; CBDCA: Carboplatin; ED-SCLC: extensive disease small-cell lung cancer; LD-SCLC: limited disease small-cell lung cancer; RT: Radiation therapy; PS: performance status.

OS in patients without liver metastasis (11.2 [95% CI 8.2–13.6] vs 10.5 months [95% CI 8.6–11.9], HR 0.75 [95% CI 0.59–0.95]) and in those with a platinum resistant disease (7.0 [95% CI 4.9–9.4] vs 5.7 months [95% CI 4.7–7.3], HR 0.71 [95% CI 0.54–0.94) compared to chemotherapy.

Pembrolizumab is a humanized IgG4 monoclonal antibody directed against PD-1. A phase Ib randomized trial (KEYNOTE-028) screened progressive SCLC patients for PD-L1 expression (PD-L1 > 1% on tumor cells/inflammatory cells or stroma) [32]. Primary endpoint were safety and ORR, while secondary objective was definition of efficacy by PFS and OS. Among the 145 screened patients, 46 (31.7%) were PD-L1 positive, but only 24 were finally treated with pembrolizumab at 10 mg/kg every 3 weeks. The ORR according to RECIST criteria v1.1 was 33.3% (95%IC 16–55%) with a median DOR of 19.4 months (range ≥ 3.6 – ≥20.0 months). The PFS rate at 6 months (PFS6) and 12 months (PFS12) was 28.6% and 23.8%, respectively, while 6-month OS (OS6) and OS12 rate was 66.0% and 37.7%, respectively. Pembrolizumab was well tolerated, even though one treatment related death due to inflammatory colitis was reported.

Results from the SCLC cohort of KEYNOTE-158 were presented at the 2018 ASCO annual meeting [33]. In this phase II trial, 107 recurrent SCLC patients were treated with pembrolizumab 200 mg flat dose every three weeks, irrespective of PD-L1 status. The primary endpoint of the study was ORR, while DOR, PFS, and OS were secondary endpoints. In the study population, 85 patients (79%) had received up to 2 prior therapy lines and 42 patients (39%) had PD-L1-positive SCLC, while 50 patients (47%) were PD-L1-negative. PD-L1 positivity was assessed using the anti-PD-L1 antibody clone 22C3 on pharmDx assay. According to PD-L1 status, ORR was significantly higher in patients with PD-L1-positive tumors (35.7%) than in those with PD-L1-negative ones (6.0%), confirming its role as predictive factor of response. Furthermore, median OS was 14.6 (95% CI 5.6-not estimable) and 7.7 months (95% CI 3.9–10.4) in patients with PD-L1-positive and PD-L1-negative tumors, respectively. Treatment-related toxicities in 59% of patients and one death due to immune-related pneumonia were reported.

Pooling together data from 83 patients treated with pembrolizumab as third- or further-line of treatment in the KEYNOTE-158 or KEYNOTE-028, FDA have recently approved pembrolizumab at a 200 mg flat dose every 3 weeks as third-line treatment in SCLC [44]. In these patients, ORR was 19% (N = 16, 95% CI 11–29%) with 94%, 63% and 56% of responses lasting 6 months, 12 months and 18 months or longer, respectively. Serious adverse events occurred in 31% of patients, most frequent being pneumonia and pleural effusion, and led 9% of patients to discontinue treatment due to toxicity.

Based on both positive toxicity profile and evidence of clinical activity in NSCLC with durvalumab, a human immunoglobulin G1 kappa monoclonal antibody directed against PD-L1, a phase I/II study of this agent was led in SCLC, whose primary endpoint was safety and secondary endpoint was activity (NCT01693562) [34]. The study enrolled 21 progressive SCLC patients not selected by PD-L1 expression and showed durvalumab to be safe in this population. The ORR, according to RECIST v1.1, was 9.5% (95% CI 1.2–30.4%), mOS was 4.8 months (95% CI 1.3–10.4) and OS12 was 27.6% (95% CI 10.2–48.4%).

Atezolizumab, a fully humanized IgG1 anti-PD-L1 antibody, was investigated in the French IFCT-1603 study, a randomized non-comparative phase II trial in SCLC patients progressing after platinum etoposide chemotherapy [38]. In this trial, 73 patients were randomized in a 2:1 fashion to receive either atezolizumab 1200 mg intravenously every 3 weeks (49 patients) or chemotherapy (topotecan or platinum-etoposide rechallenge according to platinum sensitivity, 24 patients). The primary end point was ORR at 6 weeks. The secondary end points included OS, PFS and toxicity. Unfortunately, the results of this trial were disappointing. In the intention-to-treat (ITT) population, ORR at 6 weeks was 2.3% (95% CI 0.0–6.8%) in the atezolizumab group compared to 10% (95% CI 0.0–23.1%) in the chemotherapy group. Similarly, mPFS was 1.4 months (95% CI 1.2–1.5) versus 4.3 months (95% CI 1.5–5.9) and mOS was 9.5 months (95% CI 3.2–14.4) versus 8.7 months (95% CI 4.1–12.7) in the atezolizumab and the chemotherapy group, respectively. Toxicity profile was very manageable in the atezolizumab arm and no adverse event leading to atezolizumab discontinuation was reported. There was no correlation between outcome and PD-L1 expression on immune infiltrating cells, while there was only 1 sample showing tumor PD-L1 expression precluding any meaningful analysis.

Moving to the first-line setting, a recent phase II study enrolled 45 patients with non-progressive metastatic SCLC after 4–6 courses of first-line platinum-etoposide chemotherapy to receive pembrolizumab 200 mg every three weeks as maintenance therapy [45]. Primary endpoint was PFS. In the whole population, ORR was 11.1% (95% CI: 4.8–23.5%), while median PFS and OS were 1.4 months (95% CI: 1.3–2.8) and 9.6 months (95% CI: 7.0–12.0), respectively. The treatment was well tolerated in this setting, with no new safety concerns.

PD-L1 status was determined by the Dako 22C3 antibody staining on tumor cells, according to a modified proportion score, and on stromal cells. Tumors were considered PD-L1-positive when both tumor cells and mononuclear cells within the tumor cell nests stained for PD-L1. Among the 31 evaluable patients, only 3 patients were PD-L1-positive (9%). These patients had a remarkably long PFS (10, 11 and 13 months) compared to the median PFS of the overall population (1.4 months). Of the 2 patients with measurable disease, both showed a partial response on pembrolizumab. However, the small sample size did not allow any meaningful conclusion. In the same study, the presence of a lichenoid pattern of PD-L1 membrane-stained cells surrounding the tumor nests was used to consider stromal interface positive for PD-L1. According to this criterion, 8 out of 20 evaluable patients had stromal PD-L1 positivity. ORR was improved in stromal PD-L1-positive (37.5%) than in negative ones (8.3%), as well as median PFS (6.5 months [95% CI: 1.1–12.8] vs 1.3 months [95% CI: 0.6–2.5], respectively) and mOS (12.8 [95% CI: 1.1–17.6] and 7.6 months [95% CI: 2.0–12.7], respectively). Considering data from trials with single agent ICIs, the role of PD-L1 alone as predictive biomarker is still uncertain. In fact, responses have also been observed in PD-L1 negative patients receiving nivolumab monotherapy, representing the great majority (68%).

Combinations of immune checkpoint inhibitors

Different immune checkpoints play distinct roles in the immune cycle. In fact, CTLA-4 is important in the priming phase of the immune response, leading to the activation of T cells in the lymphoid compartment, while the PD-1/PD-L1 axis in the effector phase occurring in peripheral tissues, especially in tumor microenvironment. This evidence supports the hypothesis of combining anti-CTLA-4 with anti-PD-1/PD-L1 monoclonal antibodies. In SCLC, the association of ipilimumab and nivolumab has been investigated in two of the arms of the CheckMate-032 [31]. In this phase I/II trial, 61 relapsed SCLC patients received nivolumab at 1 mg/kg combined with ipilimumab 3 mg/kg (Nivo1Ipi3), while 54 patients received nivolumab at 3 mg/kg in combination with ipilimumab at 1 mg/kg (Nivo3Ipi1). Patients were eligible irrespective of PD-L1 status. PD-L1 expression was assessed retrospectively by a Dako assay using the 28–8 anti-human PD-L1 antibody clone. Tumors were considered PD-L1-positive when staining of tumor-cell membranes (at any intensity) was observed in a section that included ≥100 evaluable tumor cells. Primary endpoint of the phase I was to determine the safety and appropriate dose combination for the phase II part whose primary endpoint was ORR.

The ORR, according to RECIST v1.1, was 23% and 19% in the Nivo1Ipi3 and Nivo3Ipi1 arms, respectively. Responses were observed irrespective of both PD-L1 positivity, at each of the two cut-offs tested (1% and 5%), and platinum sensitivity. The ORR was 22% in the overall population, and 26% and 15% in platinum-sensitive and platinum-resistant patients, respectively.

Response rates in platinum-sensitive vs platinum-resistant SCLC were 28% vs 17% and 19% vs 10% in the Nivo1Ipi3 and Nivo3Ipi1 groups, respectively. Adverse events were observed more often in the Nivo1Ipi3 arm than in the other arms, confirming the higher toxicity of ipilimumab, especially when combined with other ICIs. Treatment-related neurological adverse events were observed both with nivolumab single arm and in combination arms: autoimmune encephalitis and myasthenia gravis have been already reported, but the high frequency in this trial might be related to the tendency of SCLC patients to develop paraneoplastic neurological syndromes. All this considered, toxicity profile appeared to be manageable.

The combination of ipilimumab and nivolumab is also currently under evaluation as maintenance therapy after standard therapy in localized SCLC (STIMULI trial, NCT02046733) (Table 2), whereas in metastatic setting (CheckMate-451 trial, NCT02538666) this strategy failed. The results of CheckMate-451 have been recently presented at the ELCC 2019 [46]. In this phase III study, 834 metastatic SCLC patients not progressed following four cycles of platinum-based first-line chemotherapy were randomized (1:1:1) to receive: nivolumab 1 mg/kg and ipilimumab 3 mg/kg (279 patients) every 3 weeks for a maximum of four doses and followed by nivolumab 240 mg flat dose every 2 weeks, nivolumab 240 mg (280 patients) every 2 weeks as single agent, or placebo (275 patients). The treatment was continued until disease progression, unacceptable toxicity or for a maximum of 2 years, whichever occurred first (Table 1). The primary end-point of the study was OS for nivolumab plus ipilimumab versus placebo. Secondary end-points were OS for nivolumab versus placebo and PFS for both combination strategy and nivolumab single agent versus placebo. Overall population was well-balanced among the three treatment arms. After a minimum follow-up of 9 months, the study failed to demonstrate a significant improvement in OS by the addition of nivolumab and ipilimumab (9.2 months [95%CI 8.2–10.2]; HR 0.92 [95%CI 0.75–1.12], p = 0.37), nivolumab monotherapy (10.4 months, [95%CI 9.5–12.1] HR 0.84 [95%CI 0.69–1.02]) versus placebo (9.6 months [95% CI: 8.2–11.0]). A subgroup analysis showed that a shorter time from the last dose of first-line chemotherapy to randomization (≤5 weeks) may be associated with improved OS only in patients receiving single agent nivolumab (12.1 months [95% CI: 9.6–16.1], HR 0.66 [95%CI 0.49–0.91]). The safety profiles of ICIs arms were consistent with previous reports and nivolumab was confirmed to have a better toxicity profile than nivolumab plus ipilimumab combination. In combination arm, 86% of enrolled patients had at least a treatment-related adverse event (TRAE) (52% of grade ≥ 3), 37% of them a serious TRAE (31% of grade ≥ 3) and 29% had a TRAE leading to discontinuation. In nivolumab arm, 61% of enrolled patients had at least a TRAE (12% of grade ≥ 3), 6% of them a serious TRAE (4% of grade ≥ 3) and 8% had a TRAE leading to discontinuation. The most frequent TRAEs (≥15%) in any group were diarrhea, pruritus, rash, fatigue and decreased appetite. Treatment-related deaths were reported in all three arms: 7 (2%) in nivolumab plus Ipilimumab group, 1 (< 1%) in nivolumab group and 1 (< 1%) in placebo group [46].

Recently, results from the cohort A of the Baltic study (NCT02937818) have been reported [35]. In this study, recurrent platinum-refractory metastatic SCLC patients were treated with durvalumab 1500 mg flat dose plus tremelimumab, a fully human IgG2 antibody against CTLA-4, 75 mg flat dose, every 4 weeks for 4 months followed by maintenance therapy with durvalumab alone. Primary endpoint of the study was ORR, while PFS and OS were secondary endpoints. Among the 21 treated patients, ORR was 9.5% (95%CI 1.17–30.38) with a tolerable safety profile.

Combination of immune checkpoint inhibitors and chemotherapy

Preclinical data showed that chemotherapy may increase the release of tumor-specific antigens, boosting the MHC-I mediated T cell activation and enhancing T-cell-mediated killing of tumor cells. Chemotherapy has also been reported to increase the antitumor activity of ipilimumab in a synergistic fashion [47,48]. The synergism of activity between cytotoxic agents and ICIs could find a further explanation in the role of myeloid-derived suppressor cells (MDSC). Preclinical data have shown that chemotherapy can decrease the number of MDSC, reported to be one of the players in the suppression of immune response, by inhibiting T cells and NK cells activity. 5-Fluorouracile, docetaxel and cisplatin are some of the drugs able to impair MDSC immunosuppressive activity [49].

In a randomized, double-blind phase II study, 130 chemotherapy-naive metastatic SCLC patients were randomized to receive paclitaxel/carboplatin with or without (control arm) ipilimumab. Ipilimumab was administered using two different schedules: concurrent (four doses of ipilimumab 10 mg/kg + paclitaxel 175 mg/mq and carboplatin AUC 6 followed by two doses of placebo + paclitaxel/carboplatin) or phased (two doses of placebo + paclitaxel 175 mg/mq and carboplatin AUC 6, followed by four doses of ipilimumab 10 mg/kg + paclitaxel/

carboplatin) [37]. A longer OS was observed in the phased-ipilimumab arm when compared to the concurrent and the placebo arm, but this difference was not statistically significant (median, 12.9 versus 9.1 months versus 9.9 months; HR, 0.75; p = 0.13). Similarly, ORR according to immune-related response criteria (irRC) was numerically superior in the phased-ipilimumab arm (71%) when compared to the concurrent (49%) and placebo arm (53%).

Following these results, a phase III randomized trial compared platinum plus etoposide with or without ipilimumab in patients with newly diagnosed metastatic SCLC [50]. Despite initial positive findings, no benefit in terms of OS, the primary endpoint, from the addition of ipilimumab was observed (11 months vs 10.9 months, respectively; HR 0.94, 95%CI 0.81–1.09; p = 0.38).

More recently, results from IMpower-133 study have been reported. This was a double-blinded, placebo-controlled phase III trial designed to evaluate the safety and efficacy of atezolizumab in combination with standard first-line chemotherapy, in respect to placebo plus the same regimen in treatment-naïve metastatic SCLC patients [51]. Four-hundred and three patients were randomized to receive standard first-line chemotherapy in the induction phase (carboplatin AUC 5 mg/mL/min, day 1 and etoposide 100 mg/mq days 1–3) plus atezolizumab 1200 mg administered intravenously every 3 weeks for 4 cycles or placebo (control arm). The induction phase was followed by a maintenance phase when patients could continue atezolizumab or placebo according to the previous assignment. Co-primary endpoints were PFS and OS and both were reached. Median PFS was 5.2 (95% CI 4.4–5.6) and 4.3 months (95% CI 4.2–4.5) in the atezolizumab and the placebo arm, respectively, with 23% reduction of the risk for disease progression or death with atezolizumab compared to placebo (HR 0.77, 95%CI 0.62–0.96, p = 0.02). Median OS was longer (12.3 [95%CI 10.8–15.9] vs. 10.3 months [95%CI 9.3–11.3], HR 0.70, 95%CI 0.54–0.91; p = 0.0069) and OS12 was higher (51.7% [95% 44.4–59.0%] vs. 38.2% [95%CI 31.2–45.3%]) in the atezolizumab than in the placebo arm, respectively. A 30% reduction for the risk for death was observed. The benefit associated with atezolizumab compared to placebo was consistent across the subgroups analyzed. The ORR and median DOR were similar between the two arms, but a numerically higher percentage of ongoing responses at data cutoff was reported in the atezolizumab than in the placebo arm (14.9% vs 5.4%, respectively), even though this difference did not achieve statistical significance. Similar rates of treatment-related toxicity were observed in the two arms. In particular, treatment-related adverse events occurred in 94.9% and 92.3% of patients in the atezolizumab and placebo arm, respectively. Immune-related adverse events occurred in 39.9% of patients in the atezolizumab arm, most common being rash (18.7%) and hypothyroidism (12.6%). Interpretation of these results should take into account the favorable prognostic characteristics of the enrolled population, given the exclusion of poorer performance status patients, which are common among SCLC patients, and the relatively low frequency of patients with baseline brain metastasis (9% overall) compared to what previously reported [52,53]. All these considered, this study represents an important achievement in the field of SCLC treatment, since atezolizumab is the first agent leading to a survival improvement in the last 30 years.

The CASPIAN study is an ongoing similar phase III trial of durvalumab with or without tremelimumab in combination with platinum-based and etoposide chemotherapy in first-line metastatic SCLC (NCT03043872). Recently, a pre-planned interim analysis conducted by an Independent Data Monitoring Committee reported an improvement in OS in the durvalumab + platinum-based and etoposide chemotherapy in respect to the chemotherapy alone control arm [54].

Similarly, the KEYNOTE-604 is a trial of platinum-based and etoposide chemotherapy and pembrolizumab (NCT03066778) whose primary endpoint is OS.

Predictive biomarkers

Identification of a reliable biomarker is crucial in immunotherapy and especially in SCLC. The small benefit observed in the IMpower-133 trial and the crossing curves in the CheckMate-331 resemble the presence of a subset of patients who benefits from immunotherapy that we are not properly selecting to date. Efforts have been made to identify predictive biomarkers of response to immunotherapy in SCLC in order to assign the right patient to the right treatment, i.e. the one that optimizes patients' likelihood of having benefit and minimizes that of having harm. The detection of serum autoantibodies was evaluated in a phase II study of SCLC patients on carboplatin and etoposide with ipilimumab as first-line treatment [55]. In this study, the presence of serum autoantibodies did not perform well as a predictive biomarker, even though there was a not significant correlation between its presence and response to therapy (p = 0.066). The presence of positive serum autoantibodies showed a prognostic value rather than a predictive one. In fact, a longer median PFS was observed in patients with positive autoantibodies at baseline (8.8 vs 7.3 months, p = 0.036), including also antinuclear antibodies (10.2 vs 6.9 months, p = 0.032).

PD-L1 expression in SCLC cells is reported to be less frequent than in NSCLC (10–40% vs 66%) [31–33]. In SCLC, the usefulness of PD-L1 as a predictive factor of response to immunotherapy mainly comes from the *KEYNOTE* trial series. In these trials, according to analysis performed as part of the KEYNOTE-001 [56], tumors were defined PD-L1-positive when a membranous staining was observed in ≥1% of tumor and associated inflammatory cells or in stroma (proportion score), by using the anti-PD-L1 antibody clone 22C3 (Merck) on Dako platform. Samples were considered adequate if there were at least 50 viable neoplastic cells.

KEYNOTE-028 was a phase Ib multicohort trial that assessed safety and activity of pembrolizumab in different solid tumors selected for positive PD-L1 status [32]. 87.5% of patients included in the SCLC cohort was heavily pretreated (≥2 or more prior treatments) and in this selected population the results were very encouraging. However, some considerations are warranted. In this trial, enrolled patients were favorably selected given their good performance status that made them able to receive a third-line treatment. In addition, no information about known prognostic factors for SCLC patients, such as burden of visceral disease, hemoglobin, albumin and sodium levels, was reported. We do not know whether the promising performance of the study was dependent on a better prognosis in PD-L1 positive patients or not. Finally, the lack of these data, along with the good selection of patients, could limit the value and the applicability of these results in clinical practice.

It should also be considered that the difference in OS between contemporary [32] and past trials in SCLC [6,57] (9.7 months vs 26 weeks) could be solely related to the overall progress of medical care, rather than by improvements in cancer-specific treatments. This is also referred to as the non-contemporaneous bias.

Furthermore, the presence of PD-L1 expression on both immune and tumor cells, reported as composite proportion score (CPS), has demonstrated a better correlation with response [58]. An exploratory analysis showed that in SCLC, despite the low prevalence of PD-L1 expression on tumor cells, its expression on stroma may be more frequent and a possible predictive biomarker of benefit from pembrolizumab [45] and may warrant further analyses.

While PD-L1 positivity showed to be a potential predictive biomarker of response to pembrolizumab, waiting for prospective and independent validation, it was not the same in clinical trials with nivolumab. Among all patients enrolled into CheckMate-032 study and evaluated for PD-L1, ORR was not different between PD-L1-positive and PD-L1-negative groups (10% and 11%, respectively). This data supports the hypothesis that PD-L1 expression cannot be assumed as unique criterion to predict which population will benefit from anti-PD-1 antibodies, since clinical benefit from immunotherapy agents is also observed in patients with PD-L1-negative tumors.

PD-L1 evaluation still has several limitations in SCLC. Biological samples often have scarce cellularity and diagnosis is thus based on cytological analysis. Moreover, it is still not clear how PD-L1 expression is best evaluated: PD-L1 expression on stromal cells, including tumor-associated macrophages and tumor-infiltrating lymphocytes (TILs), could be more representative of effector T cells in tumor microenvironment that are inhibited by PD-L1 expression at the stromal interface [59].

The slight differences between nivolumab and pembrolizumab can be due to the assessment of PD-L1 expression. This does not depend on the antibody involved since the most used assays have the same sensitivity, as proved by the first part of the Blueprint project [60], and more recently, by its second part [61]. However, other characteristics should be considered. In nivolumab trials, only tumor cells are counted as PD-L1-positive and sample must contain at least 100 evaluable tumor cells. On the other hand, proportion score in pembrolizumab trials considered infiltrating host cells as well, and samples were considered adequate if they have at least 50 evaluable cells. Therefore, it is possible that in nivolumab trials, PD-L1 status may have been considered not assessable or negative in samples with less than 100 cells or because the anti-PD-L1 antibody stained immune host cells more than tumors cells. In both cases, those samples could have been considered assessable, if not even positive, according to pembrolizumab proportion score criteria. We do not know if this difference is enough to explain the different predictive power of PD-L1 testing in nivolumab and pembrolizumab trials.

TMB is defined as the total number of non-synonymous mutations within a tumor genome and can be considered as a surrogate for the load of neoantigens expressed by the tumor. Its role as a biomarker of response to ICIs was already highlighted for melanoma [26] and NSCLC [62]. In SCLC, a report on TMB assessed by targeted NGS in a retrospective series [63] and a further analysis of patients enrolled into CheckMate-032 study explored its possible value in SCLC [64].

Of the 401 SCLC patients in the Nivo3 (245 patients) and the Nivo1Ipi3 group (156 patients), whole-exome sequencing (WES) was successfully performed in a remarkably high proportion of patients (53%, N = 211). In this study, TMB groups were defined according to tertiles: < 143 mutations (low), 143–247 (medium), ≥248 (high). According to TMB groups, ORR in the Nivo3 group was 21.3%, 6.8% and 4.8% in the high, medium and low TMB group, respectively, while in the Nivo1Ipi3 group ORR was 46.2%, 16.0% and 22.2%. A similar distribution is reported to be observed whether patients are grouped by quartiles or by median, thus reducing the possibility of a post-hoc analysis bias. Moreover, ORR was higher in patients receiving Nivo1Ipi3 than in those receiving Nivo3 within each TMB group. A higher TMB was also associated with higher PFS12 and OS12. In fact, in the Nivo3 group, estimated PFS12 was 21.2%, 3.1% and not calculable in the high, medium and low TMB group, respectively, while in the Nivo1Ipi3 group, the estimated PFS12 was 30%, 8.0% and 6.2%. Similarly, in the Nivo3 group, estimated OS12 was 35.2%, 26.0% and 22.1% in the high, medium and low TMB group, respectively, while in the Nivo1Ipi3 group, the estimated OS12 was 62.4%, 19.6% and 23.4%.

The role of TMB as a predictive factor for nivolumab and the combination of nivolumab and ipilimumab is strengthened by two further observations: TMB was higher in patients achieving complete or partial response with either therapy in respect to those with stable or progressive disease; TMB did not correlate with OS in an independent cohort of patients who did not receive immunotherapy [17]. In contrast, the feasibility of TMB evaluation could be affected by the nature of tumor samples which mainly derive from cytological smears in SCLC and are not always sufficient for a successful sequencing in standard clinical practice.

TMB was assessed also in IMpower-133 study population [51] by a blood-based assay on cfDNA sequenced on Illumina NGS platform [65]. TMB was determined in 351 (87%) of all patients and grouped according to two prespecified arbitrary cut-offs of 10 and 16 mutations/Mb. A TMB higher than 10 mutations/Mb and higher than 16 mutations/Mb was present in 59% and 23.1% of all enrolled patients, respectively. Of note, TMB did not correlate with ORR, PFS and OS in this trial.

While prospective confirmation is needed, little is known about the best way to assess TMB. Available data suggest that it may behave as a continuum biomarker and that a cut-off may be identified. The total number of mutations itself has been arbitrarily chosen: would the number of mutations per megabase or the log of mutations better fit with response? Or maybe only neo-antigens generating mutations should be considered? In these considerations, the rapid clinical evolution of SCLC should be taken into account since time-consuming techniques may have limited applicability in a real-world scenario.

Future perspectives

Several phase III studies are now investigating further combination of ICIs or ICIs with chemotherapy and their results are eagerly awaited (Table 2).

In the locally advanced setting, the ADRIATIC study (NCT03703297) is a placebo-controlled phase III trial of maintenance durvalumab with or without tremelimumab after platinum-based chemotherapy + etoposide and concurrent radiation therapy in non-progressing SCLC patients, which mirrors the PACIFIC trial in NSCLC [66]. Primary endpoints are PFS and OS, while correlation of TMB measured on tumor or blood samples with ORR is notable among secondary endpoints.

The anti-PD-L1 avelumab is now under investigation in a phase Ib/II trial in combination with other ICIs in the JAVELIN Medley study (NCT02554812): in the SCLC cohort, avelumab will be administered together with utomilumab, an anti-4-1BB antibody, with the aim of defining safety, pharmacokinetics, pharmacodynamics and clinical activity.

In the phase II TRINITY study, single-agent Rova-T yielded an ORR of 18% in pretreated SCLC patients [67], so that further phase III studies as second-line therapy (TAHOE study: vs topotecan for DLL3 > 75%, NCT03061812) and as maintenance therapy (MERU study: vs placebo, NCT03033511) were started. However, the accrual for the TAHOE study was stopped after independent data monitoring committee recommendation due to shorter OS in the experimental arm compared to the topotecan control arm [68]. Nonetheless, safety of the association of Rova-T and nivolumab, with or without ipilimumab, is also under evaluation (NCT03026166).

Combination of ICIs with other treatment modalities, such as radiotherapy, are also being investigated. In a phase II study, atezolizumab is administered after hypofractionated sub-lethal dose of radiation therapy in SCLC patients progressing or recurring after a first-line platinum-based chemotherapy (NCT03262454). This study is based on the evidence that hypofractionated-sublethal dose of radiation can enhance the effect of anti-PD-L1 [69], by priming T cell effector function against cancer cells, exploiting the so-called abscopal effect: this is defined as the ability of radiation therapy delivered to a local site to induce responses outside of the radiation field [70].

Deepening of tumor biology knowledge is unraveling DDR connection to immune system and response to immunotherapy [71]. This applies to the correlation between DDR defects and DNA mutations accumulation leading to a higher TMB, but also to DDR capability to recruit immune system [72]. Given SCLC reliance on DDR machinery [17], DDR proteins are also explored as treatment target. In this setting, a phase II trial of durvalumab and olaparib, an orally-available PARP inhibitor, in relapsed SCLC has been led [73], whose primary endpoint was ORR. This study was stopped early for futility after 20 patients had been enrolled: only two responses were observed (ORR 10.5%, 95%CI 1.13-33-1) out of the 4 needed to proceed to the second stage of the study. Patients were not biomarker-selected, but mandatory pre-treatment and optional on-treatment biopsies were performed. Exploratory

analysis on PD-L1 expression and pattern of T cell infiltration, showed that responses occurred irrespective of PD-L1 expression, while all tumors with T-cell-inflamed tumor infiltration on pre-treatment biopsy responded to treatment. Further definition of correlation between DDR machinery and immune system will possibly provide new predictive biomarker of response or resistance to either immunotherapy or DDR inhibitors combinations with other treatments.

Neurological immune-related adverse events (irAEs) are reported in mentioned SCLC trials [31,51] and in general in 1% of patients receiving ICIs, irrespective of underlying cancer [74]. Neurological irAEs occur significantly more frequently with anti-PD-1/PD-L1 than CTLA-4 ICIs and are usually reversible with prompt use of steroids. However, fatal neurological irAE cases account for 15% of all fatal irAEs associated with anti-PD-1/PD-L1 ICIs treatment [75]. Occurrence of neurological irAEs in SCLC may be due to the same molecular similarity between cancer cells antigens and self neuronal antigens that underlies the development of paraneoplastic syndromes in SCLC. Whether neurological irAEs are associated or more likely with baseline positive autoantibodies or paraneoplastic syndrome is unknown so that to date there is no data about prevention of these irAEs.

Conclusions

Since 2015, when immunotherapy revolutionized cancer care, clinical trials on immune-oncology agents produced a huge amount of data. Nowadays, ICIs represent a standard of care for several solid tumors such as malignant melanoma, NSCLC, kidney cancer, head and neck cancer, urothelial cancer, Merkel-cell carcinoma and tumors with high microsatellite instability.

Results in SCLC have been so far disappointing, with nothing but signals of activity suggesting that a better selection of patients based on one or more reliable predictive biomarkers could provide that breakthrough eagerly awaited in this cancer.

Expression of PD-L1 does not predict response to ICIs to date, but selection based on this biomarker seems to enrich for patients more likely to benefit from pembrolizumab.

On the other hand, TMB is overall associated with response to ICIs, especially to combination of anti-CTLA4 and anti-PD-1, such as ipilimumab and nivolumab. Limitations are tumor DNA availability in SCLC and the lack of a universally applicable cutoff. Blood-based TMB assessment could help overcome the first limitation [51,65].

Targeting DDR machinery may be potentially useful in SCLC, possibly as a combination strategy with chemotherapy or immunotherapy.

Nevertheless, the extremely high response rate to first-line chemotherapy makes it more difficult to evaluate results of clinical trials of new agents, especially in early phase trials when activity endpoints (e.g. ORR or PFS) are used as surrogate of clinical benefit.

In conclusion, immunotherapy was not so far the awaited breakthrough in SCLC, but it has been the first strategy to improve OS in this population [51].

However, since different trials showed that improvements are limited to a small proportion of patients, further efforts should be made to identify those patients most likely to benefit from immunotherapy, as observed in other settings [43,51,76–78].

In the future, early phase clinical trials should be designed with the aim to evaluate the activity of new anticancer drugs around the development of predictive biomarkers in order to optimize patients' selection. In the next years, SCLC treatment might be desirably based on a biomarker-driven selection thanks to data from ongoing and next studies.

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Declaration of Competing Interest

Authors declare they have no conflict of interest to disclose.

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