Prospects of targeted and immune therapies in SCLC

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REVIEW

Prospects of targeted and immune therapies in SCLC

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ABSTRACT

Introduction: Small cell lung cancer (SCLC) is a tumor with a poor prognosis, often diagnosed in an advanced stage. Despite aggressive treatment of early and locally advanced disease, SCLC often relapses. First line chemotherapy provides good response rates in advanced disease, but progression free and overall survival are limited. New drugs such as some targeted therapies and immune therapies are promising in SCLC.

Areas covered: In this review, we discuss the preclinical rationale and trial data for targeted therapies and immune therapies in SCLC, with a specific focus on clinical trials.

Expert commentary: Lack of identification of clear prognostic and predictive biomarkers has limited the advances in treatment efficacy. This has most likely been the main cause of failure for compounds tested so far. Due to the highly mutational profile and the rapid growth pattern of SCLC, immunotherapy combined with chemotherapy seems the most promising treatment option. Concerning targeted agents, achievements made so far are small, but DLL3-antibodies or combinations of PARPi and immunotherapy could be very promising. These promising strategies also need testing in limited disease.

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1. Introduction

Incidence of small-cell lung cancer (SCLC) has declined over the last years, especially in countries with effective smoking cessation programs (usually high-income countries); nevertheless, it still accounts for approximately 10–15% of all lung cancer cases [1]. Most importantly, SCLC is the sixth most common cause of cancer-related mortality [2] and its incidence is increasing in the low- and middle-income countries [3,4].

The strongest risk factor for developing SCLC is smoking; in an epidemiologic study, only 2.5% of the SCLC occurred in never-smokers [5]. Smoking cessation results in a decreased risk, but the risk remains higher compared to never-smokers [6–8].

Low-dose computed tomography screening for SCLC has not proven to be effective because of the highly aggressive nature of the disease [9–11]: up to 86% is diagnosed at an advanced stage, median overall survival (OS) is only 20.6 months, and no survivors were found at 3 years in a screening trial [10].

Standard treatment for SCLC has not changed over the last 10–15 years both for limited disease (LD) and extensive disease (ED). Currently, advised treatment, by European Society for Medical Oncology (ESMO) guidelines, for patients with LD is chemoradiation followed by prophylactic cranial irradiation (PCI); surgery is an option in T1–T2, N0, and M0 patients [12].

Concerning ED, standard of care is platinum-based doublet with etoposide (in Europe/US) or irinotecan (in Japan) for 4–6

cycles; PCI is an option in these patients [12]. Cisplatin can be substituted by carboplatin; as in a meta-analysis published in 2012 by Rossi *et al.*, no differences in efficacy was found [13].

Despite the high response rate (RR), most patients relapse within 6 months. The only approved second-line treatment in Europe and the USA is topotecan either intravenous or oral (similar efficacy) [14,15]. For those patients that instead progress after 6 months, a valid option is rechallenge with a platinum-based regimen.

Among other possible options, paclitaxel showed a RR of 24–29% in two small studies ($N = 21$ and $N = 24$), median OS was only 3.3 months in one trial and 5.8 months in the other trial [16,17]; temozolomide monotherapy showed a RR of 12–23% in two small trials, median OS was 5.8 months in both trials [18,19]. CAV still remains also an option although very limited due to its toxicity profile [12].

Amrubicin, approved in Japan, did not demonstrate an OS benefit compared to topotecan in the phase III European trial: median OS was 7.5 months for amrubicin and 7.8 months for topotecan (HR 0.88, $p = 0.17$), although in a subset analysis including platinum-refractory patients a numerically, significant OS improvement was found (6.2 vs 5.7 months, HR 0.77, $p = 0.47$) [20].

In this review, we will focus on the current evidence for targeted agents and immunotherapy trials and also give some insight on the promising compounds that might hopefully change the poor prognosis of the SCLC patient population.

2. Targeted therapy in SCLC

2.1. Preclinical rationale

2.1.1. Molecular alterations

The druggable alterations that are found in NSCLC are generally very rare in SCLC. For example, epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase, human epidermal growth factor receptor 2, *cMET*, v-RAF murine sarcoma viral oncogene homolog-B (*BRAF*), and c-ROS oncogene 1 (*ROS1*) mutations/translocations are rarely found in SCLC samples [21,22]. Alterations more often found in SCLC are aberrations in cell cycle regulation (e.g. *CDKN2A*, *CDK4/6*, *TP53*, *RB1*, *Chk-1*, *Wee-1*), receptor kinase signaling [e.g. stem-cell factor receptor tyrosine kinase (*c-KIT*), *PI3K/AKT/mTOR*, insulin-like growth factor receptor (*IGFR1*), fibroblast growth factor receptor 1 (*FGFR1*), *PTEN*, hedgehog signaling pathways], overexpression of the antiapoptotic proteins (e.g. *BCL-2*, found in 80% of SCLC), and alterations in DNA repair pathways [e.g. *MYC* amplification, overexpression of poly(ADP ribose) polymerase (*PARP*) enzymes, DNA alkyltransferase (*O*(6)-methylguanine-DNA methyltransferase (*MGMT*) expression] [23–30]. In contrast to other tumors, mutations in DNA repair genes (such as *BRCA1/2*) were not associated with response to *PARP* inhibition in SCLC. However, *Schlafen11* (*SLFN11*) which regulates response to DNA damage and replication stress is a possible predictive marker for response to *PARP* inhibition in SCLC, although prospective validation is needed [31]. Furthermore, epigenetic processes are also often dysregulated in SCLC (e.g. histone modifier mutations) [32]. An overview of the incidence of these alterations can be found in Sharp *et al.* [28]. Reduced SCLC tumor growth has been shown in preclinical models when the alterations mentioned above are targeted with monotherapies or combination therapies [33–40].

Another interesting target in SCLC is the NOTCH-signaling pathway, involved in early lung development and stem-cell self-renewal. NOTCH signaling can have oncogenic or tumor-suppressive effects and NOTCH can influence multiple oncogenic pathways. The function is dependent on the cellular content and tumor type; in neuro-endocrine tumors, NOTCH signaling suppresses oncogenesis and tumor growth [29,30,41–43]. One of the NOTCH inhibitory ligands is delta-like ligand 3 (*DLL3*), which is overexpressed in approximately 69% of SCLC but not in normal tissue [29,30]. This *DLL3* overexpression is caused by achaete-scute homologue 1 (*ASCL1* or *ASH-1*) which regulates NOTCH-signaling components [44,45]. *ASH-1* is a master regulator required for growth and survival of SCLC cells [46] and is expressed when the tumor-suppressor genes *TP53* and *RB1* are inactivated. Bi-allelic inactivation of the tumor-suppressor genes *TP53* and *RB1* occurs in almost all SCLC cases [29]. Preclinically, therapy with a *DLL3*-targeting antibody–drug conjugate (ADC) resulted in killing of SCLC cells, especially when they were expressing *DLL3* [47].

SCLC can be divided into three distinct molecular subtypes by gene-expressing profiles, based on expression of *ASH-1* and neurogenic differentiation factor 1 (*NEUROD1*, a neuronal master regulator) [44]. The classic SCLC form ('neuroendocrine high') is characterized by *ASH-1* expression, the classic/variant type ('neuroendocrine variable') by high *NEUROD1* expression with or

without *ASH-1* expression. The last form (variant/'neuroendocrine negative') is rare and has no expression of these two markers [44,48,49]. The different forms might respond different to immune therapies [50]. Last, although the majority of SCLC patients have mutant *RB1*, some have wild-type *RB1*, with varying percentages reported in the literature [29,51]. *RB1* status is important, as patients with wild-type *RB1* have lower responses to chemotherapy [51], and mutant *RB1* status has been associated with sensitivity to DNA-damaging agents [52].

2.1.2. Angiogenesis

Besides the abovementioned alterations, the vasculature can also be targeted in SCLC as SCLC is a highly angiogenic tumor [53–55]. Compared with healthy controls, vascular endothelial growth factor (VEGF) and ang-2 (angiogenesis mediator) are increased in SCLC patients [56,57]. SCLC cell lines also express VEGF-receptor (VEGFR) 2 and 3 [54]. Furthermore, a high level of circulating VEGF is associated with poor OS and poor response to treatment [58,59].

2.1.3. Other targets

Essential for tumor growth are sterols and isoprenoids that are produced by the mevalonate pathway; cholesterol is a component of this pathway (reviewed in Mullen *et al.*) [60]. Preclinically, it has been shown that statins can inhibit SCLC growth, either alone or in combination with chemotherapy [61].

Matrix metalloproteinases (MMPs) are a family of secreted proteins that are capable of digesting extracellular matrix and basement membrane components. MMP expression is often detected in SCLC and elevated expression has been associated with worse OS [62]. Preclinically, MMP inhibitors were able to reduce tumor growth [63,64].

Trophoblast cell-surface antigen (Trop-2) is a glycoprotein that is elevated in many types of cancer, including SCLC. Elevated Trop-2 stimulates cancer growth and is associated with a worse prognosis. Preclinically, an ADC against Trop-2 showed activity in several cancers including SCLC [65].

2.2. Trial data with targeted agents in LD-SCLC

The majority of trials have evaluated targeted therapy in advanced SCLC. The few that have tested targeted therapies in LD-SCLC are summarized in Table 1; those that included LD-SCLC as well as ED-SCLC patients are summarized only in this section and not in the ED-SCLC section. Ongoing trials are summarized in Table 2.

2.2.1. Angiogenesis

Thalidomide has antiangiogenic properties and has been evaluated in a randomized, double-blind, placebo-controlled trial (*N* = 724), including both LD- (51%) and ED-SCLC patients. Primary end point was OS. Median OS was 10.5 months for placebo and 10.1 months for thalidomide [HR (95% CI) 1.09 (0.93–1.27); *p* = 0.28]. Patients treated with thalidomide had a significantly higher risk of having a thromboembolic event (*p* < 0.001) [66].

Vanetanib is another antiangiogenic agent as well as an EGFR inhibitor and was tested as maintenance therapy in a

Table 1. Completed trials with targeted therapies in SCLC.

Author, year	Treatment	Trial type	NSCLC	Primary study objective	Outcome
Trials with targeted agents in LD-SCLC (±ED-SCLC)					
Lee, 2009 [66]	CT + thalidomide or placebo	Phase III Double blind	724 (51% LD)	OS	<i>Overall</i> Median OS 10.5 m (placebo) vs 10.1 m (thalidomide) HR (95% CI) 1.01 (0.93–1.27); $p = 0.28$ <i>LD-SCLC</i> Median OS 12.1 m (placebo) vs 13.1 m (thalidomide) HR (95% CI) 0.91 (0.73–1.15)
Arnold, 2007 [67]	CT ± TRT ± PCI followed by maintenance vandetanib or placebo	Phase II Double blind	107 (43% LD)	PFS	<i>Overall</i> Median PFS 2.7 m (vandetanib) vs 2.8 m (placebo) HR (80% CI) 1.01 (0.75–1.36); $p = 0.51$ <i>LD-SCLC</i> Median PFS 10.0 m (vandetanib) vs 6.7 m (placebo) HR (80% CI) 0.80 (1.5–1.3)
Seckl, 2017 [68]	CT + pravastatin or placebo	Phase III Double blind	846 (43% LD)	OS	<i>Overall</i> Median OS 10.7 m (pravastatin) vs 10.6 m (placebo) Adjusted HR (95% CI) 1.02 (0.89–1.18); $p = 0.76$ <i>LD-SCLC</i> Median OS 14.6 m (pravastatin) vs 14.6 m (placebo) HR (95% CI) 0.96 (0.76–1.20); $p = 0.71$
Shepherd, 2002 [69]	Maintenance marimastat or placebo after response to first-line CT	Phase III Double blind	532 (54% LD)	OS	<i>Overall</i> Median OS 9.3 m (marimastat) vs 9.7 m (placebo) HR (95% CI) 1.01 (0.83–1.23); $p = 0.90$ <i>LD-SCLC</i> Exploratory analysis no benefit of marimastat
First-line trials with targeted agents in ED-SCLC					
Pietanza, 2016 [90]	Cisplatin–etoposide + sonidegib	Phase I	15	MTD Safety	RP2D 800 mg once daily Grade ≥3 toxicities: anemia (33%), neutropenia (53%), CPK elevation (13%), fatigue (13%), nausea (13%)
Belani, 2016 [91]	CT, CT + vismodegib or CT + cixutumumab	Phase II 3-Arm, open label	152	PFS	Median PFS 4.4 m (CT), 4.4 m (CT + vismodegib), and 4.6 m (CT + cixutumumab) HR vismodegib–CT vs CT: 0.98 (0.65–1.47); $p = 0.45$
Spigel, 2011 [93]	CT + bev or placebo followed by maintenance bev/placebo	Phase II Double blind	102	PFS	Median PFS 4.4 m (placebo) vs 5.5 m (bev) HR 0.53, 95% CI 0.32–0.86
Pujol, 2015 [92]	2 Cycles of CT, followed by 2 cycles of CT + bev and maintenance bev or 2 cycles of CT and no maintenance	Phase II/III	147	% DCR at 4th cycle	DCR 89% for CT and 92% for CT + bev ($p = 1.00$)
Tiseo, 2017 [94]	CT + bev or placebo followed by maintenance bev/placebo	Phase III Double blind	204	OS	Median OS 8.9 m (placebo) vs 9.8 m (bev) HR 0.78, 95% CI 0.58–1.06; $p = 0.113$
Ready, 2015 [96]	CT followed by maintenance sunitinib or placebo	Phase II Double blind	144*	PFS from randomization to maintenance	Median PFS 2.1 m (placebo) vs 3.7 m (sunitinib) HR (95% CI) 1.62 (1.02–2.60); $p = 0.02$ Median OS 6.9 m (placebo) vs 9 m (sunitinib) HR (95% CI) 1.28 (0.79–2.10); $p = 0.16$
Second-line and beyond trials with targeted agents					
Pietanza, 2018 [72]	Temozolomide + veliparib or placebo second/third line	Phase II Double blind	104	4-month PFS	4-month PFS 36% (temozolomide + veliparib) vs 27% (temozolomide + placebo); $p = 0.19$
Rudin, 2017 [77]	Rova-T second line and beyond	Phase I	74	Safety ORR	Most common grade ≥3 TRAE: thrombocytopenia (11%), pleural effusion (8%), and increased lipase (7%) ORR 18% in patients treated at MTD
Carbone, 2018 [78]	Rova-T third line and beyond in DLL3-expressing SCLC	Phase II Single arm	339	ORR	ORR 36% in DLL3-high patients
Gray, 2017 [79]	IMMU-132 second line and beyond	Phase II single arm	50	Safety ORR	ORR 12.4% (14.3% in DLL3 high) Median OS 5.6 m (5.7 m in DLL3 high) Most common grade ≥3 TRAE: neutropenia (34%), fatigue (13%), diarrhea (9%), and anemia (6%) ORR 14%

(Continued)

Table 1. (Continued).

Author, year	Treatment	Trial type	NSCLC	Primary study objective	Outcome
Edelman, 2009 [80]	Re-188 P2045 for SCLC patients expressing somatostatin receptors	Phase I	15	Safety	Grade 3 toxicity: lymphopenia (7%), abdominal pain (7%), hyponatremia (7%) No responses
Melichar, 2015 [85]	Alisertib	Phase I/II	60	ORR	ORR 21% (platinum-refractory 25%, platinum-sensitive 19%)
Owonikoko, 2017 [87]	Paclitaxel + alisertib or placebo, second line	Phase II	178	PFS	Median PFS 3.2 (alisertib) vs 2.2 m (placebo)
Calvo, 2017 [89]	Doxorubicin + lurbinectedin	Double blind Phase I	27	Safety ORR	Adjusted HR (95% CI) 0.71 (0.51–0.99); $p = 0.038$ Most toxicity grade 1–2 Grade 4 toxicity only hematological (79% neutropenia) Grade 3 toxicity also mainly hematological, low percentage of liver test abnormalities, fatigue, infections, mucositis, and electrolyte disturbances ORR 91.7% in second-line platinum-sensitive disease; 33.3% in platinum-refractory disease ORR 20.0% third line ORR 20%
Mountzios, 2012 [98]	Paclitaxel/Bev in platinum-refractory disease	Phase II Single arm	30	ORR	3-month PFS 65%
Spigel, 2013 [99]	Topotecan + bev second line	Phase II Single arm	50	3-month PFS	ORR 25%
Trafalis, 2016 [100]	Irinotecan + bev second line	Phase II Single arm	32	ORR	ORR 5%
Han, 2016 [95]	Nintedanib second/third line	Phase II Single arm	24	ORR	Platinum-refractory 3-month PFS 27% (ziv-aflibercept) vs 10% ($p = 0.02$) Platinum-sensitive 3-month PFS 24% (ziv-aflibercept) vs 15% ($p = 0.14$) Median PFS 4.1 (anlotinib) vs 0.7 months (HR 0.19, $p < 0.001$)
Allen, 2014 [97]	Topotecan ± Ziv-aflibercept	Phase II Single arm Open label	189	3-month PFS	
Cheng, 2018 [81]	Anlotinib second/third line vs placebo	Phase II Double-blind randomized	119	PFS	

*95 Randomized to maintenance.

N: Number; SCLC: small-cell lung cancer; LD: limited disease; ED: extensive disease; CT: chemotherapy; OS: overall survival; m: months; HR: hazard ratio; CI: confidence interval; TRT: thoracic radiotherapy; PCI: prophylactic cranial irradiation; PFS: progression-free survival; MTD: maximum-tolerated dose; RP2D: recommended phase II dose; bev: bevacizumab; DCR: disease control rate; TRAE: treatment-related adverse events; Rova-T: Rovalpituzumab Tesirine; ORR: objective response rate.

Table 2. Ongoing trials with targeted therapies in SCLC.

Clinicaltrial.gov number	Stage	Phase	Primary objective	Primary end point	Treatment	Locations	Sponsor
BCL-2 inhibitors							
NCT03080311	ED	I	Safety	DLT	APG-1252	US	Ascentage
Alkylating deacetylase inhibitor							
NCT03345485	ED	I/II	Activity	ORR	Tinostamustine	US	Mundipharma
NCT02972320	ED	II	Efficacy	PFS	Temozolomide	China Medical University	China Medical University
PARP inhibitors ± other compounds							
NCT03227016	ED	I/II	Safety	DLT	Velparib + topotecan	Klinik München Gauting	Central European Society for Anticancer Drug Research
NCT03150810	ED	Ib	Safety	DLT	BGB-290 + temozolomide	US	Beigene USA, Inc.
NCT03009682	ED	II	Activity	ORR	Olaparib	Samsung Medical Center	Samsung Medical Center
NCT03532880	ED	I	Safety	MTD	Olaparib + RT	MSK	MSK
NCT03428607	ED	II	Activity	ORR	Olaparib + AZD6738	Samsung Medical Center	Samsung Medical Center
NCT02446704	ED	II	Activity	ORR	Olaparib + temozolomide	US	AZ
NCT02899728	ED	II	Efficacy	PFS	Olaparib + cediranib + CT	US	NCI
NCT02769962	ED	I/II	Activity	ORR	CRLX101 + olaparib	US	NCI
NCT02734004	ED	I/II	Activity	ORR	Olaparib + durvalumab	World	AZ
NCT02734004	ED	I/II	Activity	DCR	• Olaparib + durvalumab • Olaparib + durvalumab + bevacizumab	World	AZ
WEE1 inhibitors ± other compounds							
NCT02937818	ED	II	Activity	ORR	AZD1775 + carboplatin	World	AZ
NCT02511795	ED	I	Safety	MTD	AZD1775 + olaparib	US; Canada	AZ
NCT02482311	ED	I	Safety	MTD	AZD1775	US; Canada	AZ
NCT02593019	ED	II	Activity	ORR	AZD1775	Samsung Medical Center	Samsung Medical Center
NCT02688907	ED	II	Activity	ORR	AZD1775	Samsung Medical Center	Samsung Medical Center
Checkpoint kinase inhibitors							
NCT02735980	ED	II	Activity	ORR	Prexasertib	World	Eli Lilly
DLL3 antibodies ± other compounds							
NCT02819999	ED	I	Safety	MTD	Rova-T with/without CT	World	Stemcentrx
NCT03033511	ED	III	Efficacy	PFS	Rova-T	World	AbbVie
NCT02674568	ED	II	Activity	ORR	Rova-T	World	Stemcentrx
NCT03061812	ED	III	Efficacy	OS	Rova-T vs topotecan	World	AbbVie
NCT03026166	ED	I	Safety	DLT	Rova-T + nivolumab ± ipilimumab	World	AbbVie
Multikinase inhibitors							
NCT01935336	LD, ED	II	Activity	ORR	Ponatinib	University of Colorado	Ariad
DNA transcription inhibitor							
NCT02566993	ED	III	Efficacy	PFS	Lurbinectedin + doxorubicine vs CAV or topotecan	World	PharmaMar
EZH2 inhibitor							
NCT03460977	ED	I	Safety	DLT	PF-06821497	US	Pfizer
Aurora kinase inhibitor							
NCT03216343	ED	I	Activity	ORR	Chiauranib	Beijing Cancer Hospital	Chipscreen Biosciences

ED: Extensive disease; LD: limited disease; DLT: dose-limiting toxicity; US: United States; ORR: objective response rate; PFS: progression-free survival; MTD: maximum-tolerated dose; RT: radiotherapy; MSK: Memorial Sloan Kettering; AZ: AstraZeneca; NCI: National Cancer Institute; DCR: disease control rate; Rova-T: Rovalpituzumab Tesirine; CT: chemotherapy; OS: overall survival.

double-blind randomized phase II trial ($N = 107$), including LD- (43%) as well as ED-SCLC patients. Vandetanib did not improve progression-free survival (PFS) (primary end point): median 2.7 (vandetanib) versus 2.8 (placebo) months, respectively [HR (80% CI) 1.01 (0.75–1.36); $p = 0.51$]. Median OS (a secondary end point) was also not significantly different: 10.6 months for vandetanib versus 11.9 for placebo [HR (80% CI) 1.43 (1.00–2.05); $p = 0.9$] [67]. In both trials, also the subgroup of LD-SCLC patients did not derive benefit in the experimental arm [66,67].

2.2.2. Other targets

In the multicenter, phase III, randomized, double-blind, placebo-controlled LUNGSTAR trial ($N = 846$, 43% LD-SCLC), pravastatin 40 mg once daily or placebo was added to standard-of-care first-line treatment (chemoradiation for LD-SCLC, platinum–etoposide for ED-SCLC). Pravastatin did not significantly improve OS (primary end point): for LD patients, median OS was 14.6 months for the pravastatin group and 14.6 months for the placebo group [HR (95% CI) 0.96 (0.76–1.20); $p = 0.71$] [68].

Adjuvant marimastat (10 mg orally bid), a MMP inhibitor, has also been evaluated in a randomized, double-blind, placebo-controlled phase III trial ($N = 532$, 54% LD-SCLC). The trial was negative: median OS was 9.3 months for marimastat and 9.7 months for placebo [HR (95% CI) 1.01 (0.83–1.23); $p = 0.90$]. In an unplanned analysis, there was also no survival benefit for marimastat for the LD patients [69].

2.3. Trial data with targeted agents in ED-SCLC

2.3.1. Molecular alterations

Tyrosine kinase receptor inhibitors inhibiting cell signaling and/or apoptosis, with or without targeting angiogenesis (e.g. imatinib, dasatinib, gefitinib, linsitinib, sorafenib, sunitinib, cediranib, nintedanib, and pazopanib), all failed to show a significant benefit in SCLC (reviewed in Sharp *et al.* [28] and Baize *et al.* [70]). More promising targets are summarized in Table 1 and ongoing trials are summarized in Table 2.

2.3.2. PARP inhibitors

Temozolomide, an alkylating agent prodrug, showed some activity in a single-arm phase II trial ($N = 64$): ORR was 23% in the platinum-sensitive cohort ($N = 48$) and 13% in the platinum refractory cohort. However, median PFS was only 3.5 months [18]. There was a trend to a higher ORR in patients with MGMT promotor methylation: 38% versus 7% ($p = 0.08$).

Resistance to temozolomide can be PARP-based and there is preclinical evidence that PARP inhibitors (PARPi) act synergistically with temozolomide [37,71]. Therefore, veliparib (PARPi) 40 mg orally twice daily on day 1–7 (28-day cycle) combined with temozolomide 150–200 mg/m²/day orally once daily on day 1–5 was tested in a randomized, double-blind, placebo-controlled phase II trial including ED-SCLC patients eligible for second/third-line treatment ($N = 104$). The trial was negative for its primary end point: 4-month PFS was 36% for veliparib/temozolomide and 27% for placebo/temozolomide ($p = 0.19$). Median OS was also not significantly different also (8.2 vs 7 months, respectively, 95% CI 5.3–9.5, $p = 0.50$). Nevertheless, the combination resulted in a significantly higher ORR (39%) compared to

temozolomide-placebo (ORR 14%) ($p = 0.016$) at the price of a higher percentage of grade 3 and 4 thrombocytopenia and neutropenia (50% vs 9%, 31% vs 7%, respectively). In the exploratory biomarker analysis, in the subset of patients tested for PARP1 and/or MGMT methylation, no association between PARP1 positivity or MGMT methylation and ORR was found. Interestingly, patients with SLFN11 expression had improved PFS and OS with the veliparib/temozolomide combination [72]. As this analysis was exploratory, further evaluation is necessary to determine whether SLFN11 expression could serve as a biomarker to select SCLC patients for therapy with PARPi. Of note, a new biopsy should be obtained after chemotherapy, as SLFN11 decreases after exposure to chemotherapy [72].

Furthermore, it is possible that the combination with a PARPi and a PI3K-inhibitor would be a better combination, as SCLC can escape PARPi by upregulation of the PI3K–AKT–mTOR pathway [33]. To the best of our knowledge, no trials have been completed or are currently ongoing with this combination. Everolimus (a PI3K-inhibitor) monotherapy had limited activity [73]. Trials with veliparib added to platinum–etoposide are currently open (NCT01642251 and phase II part of NCT02289690), as veliparib potentiated the effect of platinum–etoposide preclinically and was shown to be safe in a phase I trial [74]. Olaparib is also a PARPi, and several trials of monotherapy olaparib or in combination with another drug are ongoing.

Another interesting combination is the combination of a PARPi and a Wee1 inhibitor: in a preclinical model, olaparib combined with the Wee1 inhibitor AZD1775 was more efficacious than cisplatin/etoposide in chemosensitive circulating tumor cell patient-derived explants (CDx), but responses diminished when the combination was tested at disease progression, suggestion that it should be tested in the clinic before disease progression. CDx with defects in DNA repair genes benefited most [75]. Several trials with monotherapy AZD1775 or AZD1775 combined with PARPi are ongoing in SCLC (Table 2).

Last, combination of a PARPi and a cell-cycle inhibitor is interesting as preclinically, prexasertib (LY2606368), a cell-cycle checkpoint kinase CHK1 inhibitor, combined with olaparib or cisplatin augmented the effects of the other drug, especially when MYC amplification or overexpression was present [76]. A phase II study of monotherapy prexasertib is ongoing (NCT02735980).

2.3.3. ADCs

ADCs are antibodies directed at a defined antigen on a cancer cell, linked to a cytotoxic agent. Several are in development for SCLC treatment. The most advanced are Rovalpituzumab Tesirine (Rova-T) and Sacituzumab Govitecan (IMMU-132). Furthermore, Re-188 P2045, a somatostatin analog labeled with Rhenium-188, showed interesting survival in a phase I trial.

Rova-T recognizes the NOTCH ligand DLL3. In a phase I trial (NCT01901653), 82 lung cancer patients (74 SCLC, 8 LCNEC), who progressed after one or more lines of chemotherapy, were treated with escalating doses of single-agent Rova-T. About 18% of patients treated at the maximum-tolerated dose had a confirmed response and 50% had stable disease. Activity was higher in DLL3-high patients: ORR was 38% and

disease control rate was 50%. Median OS was 5.8 months in the DLL3-high group. The safety profile was manageable; most common grade ≥ 3 toxicities were thrombocytopenia, pleural effusion, and increased lipase [77]. Based on these results, other trials with Rova-T were initiated, mainly in DLL3-high SCLC patients.

Results of the phase II TRINITY trial have recently been presented: 339 DLL3-expressing patients were included and were treated with Rova-T 0.3 mg/kg IV every 6 weeks, for 2 cycles (under specified conditions, retreatment was allowed). Primary end points were ORR and OS; a prespecified subgroup analysis included those with high DLL3 expression ($\geq 75\%$ of cells DLL3 positive). About 66% of patients completed the planned two doses of Rova-T, and ORR by independent review was 12.4% and was 14.3 in the DLL3-high group ($N = 238$). In the DLL3-high group, 72% (third-line Rova-T) and 77% (fourth line) had disease control. Median OS (95% CI) was similar and was 5.6 (4.9–6.1) months in the total group and 5.7 (4.9–6.7) months in the DLL3-high group. Responses (best response and confirmed ORR) were associated with improved outcomes, as median OS was 9.8 months for responders. Forty percent of patients had grade 3 or higher treatment-related adverse event, of interest were photosensitivity reactions, pleural effusion, peripheral edema, and pericardial effusion. Other common toxicities were mainly gastrointestinal. Three percent had fatal events (edema, pneumonitis, ascites, drug-induced liver injury, pleural effusion, pneumothorax, respiratory failure, and sepsis) [78]. Two other methods of targeting DLL3 are a half-life extended bi-specific T-cell engager antibody construct (AMG 757) and adoptive chimeric antigen receptor T-cell therapy (AMG 119); phase I trials are currently enrolling (NCT03319940 and NCT03392064, respectively).

IMMU-132 contains the active metabolite of irinotecan, conjugated to an antibody that binds to Trop-2 which is widely expressed on SCLC. In a single-arm phase II trial (NCT01631552), 50 pretreated SCLC patients were treated with IMMU-132 8 or 10 mg/kg iv on days 1 and 8 of a 21-day cycle. Primary end points were safety and ORR. Fourteen percent of patients had confirmed responses; median duration of response (DOR) was 5.7 months. Most common grade ≥ 3 toxicities were neutropenia (34%), fatigue (13%), diarrhea (9%), and anemia (6%). Median OS was 7.5 months and was not statistically significantly different for those with platinum-sensitive or platinum-resistant disease in the overall population [79].

Re-188 P2045 was tested in a phase I trial, including advanced NSCLC and SCLC patients expressing somatostatin receptors ($N = 15$, of which 14 had ≥ 2 previous treatment lines). No responses were seen, but 62.5% had stable disease for at least 8 weeks, and median OS was 11.5 months which is unexpectedly long in a pretreated population [80]. However, to the best of our knowledge, no trials are ongoing with this compound.

2.3.4. FGFR inhibitors

One trial has completed recruitment, although study results are not yet available: NCT02109016, a phase 2 study to assess if lucitanib is safe and effective (ORR) in the treatment of

patients with advanced/metastatic lung cancer and FGFR, VEGF, or platelet-derived growth factor (PDGF)-related genetic alterations.

2.3.5. Multikinase inhibitors

Anlotinib is a multikinase inhibitor, especially inhibiting VEGFR, c-KIT, PDGFR, and FGFR. This drug showed promising clinical activity in third-line treatment and beyond the randomized, double-blind phase II ALTER1202 trial (NCT03059797). Patients were randomized 2:1 to anlotinib 12 mg qd orally, days 1–14 of a 21-day schedule ($N = 81$), or placebo ($N = 38$). Median PFS (primary end point) was significantly prolonged in the anlotinib arm compared with the placebo arm: 4.1 (95% CI 2.8–4.2) months versus 0.7 (95% CI 0.7–0.8) months [HR 0.19 (95% CI 0.12–0.32), $p < 0.001$]. OS data were not sufficiently mature at the date of the first report (WCLC, September 2018). Toxicity was manageable, with 35.8% versus 15.4% grade 3–5 toxicity (1 death in the anlotinib group possibly related to anlotinib). The most common grade ≥ 3 toxicity was hypertension (13.6%), followed by hand–foot syndrome (4.9%), hypertriglyceridemia (3.7%), and lymphopenia (2.5%) [81]. Anlotinib is currently being tested as maintenance therapy after four cycles of lobaplatin/etoposide in a randomized phase II trial (NCT03700359).

2.3.6. Aurora kinase inhibitors

Aurora kinase A is necessary for mitotic spindle formation. MYC, a transcriptional regulator of aurora kinases A and B, is amplified in 9–20% of SCLCs [82,83]; these SCLCs have a growth advantage in the absence of p53 [84]. Alisertib, an aurora kinase inhibitor, showed promising results in a phase I/II trial-included patients with pretreated solid cancer. Primary end point was ORR. Alisertib was given at a dose of 50 mg twice daily, for 7 days followed by a break of 14 days. In the subgroup of SCLC patients ($N = 60$, of which 48 were response evaluable), an ORR of 21% was found. Thirty-six SCLC patients had platinum-sensitive disease and 12 had platinum-resistant disease; the highest ORR was found for platinum-refractory patients (25% vs 19%). DOR was 3.1 months for platinum-sensitive patients and 4.3 months for platinum-resistant patients. Most common grade 3–4 adverse events were neutropenia (43%), leukopenia (21%), and anemia (10%) [85].

Aurora A functional single nucleotide polymorphisms were associated with improved outcome in patients with solid tumors treated with alisertib [86]. Based on these results, a randomized phase II study was initiated in advanced SCLC, evaluating second-line paclitaxel with alisertib or placebo. Patients were stratified according to platinum-sensitive or refractory disease and the presence of brain metastases. Primary end point was PFS. Alisertib was given at a dose of 40 mg twice daily orally, 3 days on/4 days off. When combined with alisertib, paclitaxel was given at a dose of 60 mg/m² iv on days 1, 8, and 15 of a 28-day schedule. When combined with placebo, paclitaxel was given a dose of 80 mg/m². A total of 178 patients were enrolled: median PFS was significantly higher in the investigational arm and was 3.2 versus 2.2 months [corrected HR (95% CI) 0.71 (0.51–0.99); $p = 0.038$]. In the platinum-resistant group ($N = 109$), median PFS was also significantly higher in the investigational arm: 2.9 vs 1.6 months [HR (95% CI)

0.66 (0.44–0.98); $p = 0.037$]. ORR was slightly higher in the alisertib/paclitaxel group: 22% versus 18%. There was a trend to a significantly higher median OS in the investigational arm: 6.9 versus 5.6 months [HR (95% CI) 0.73 (0.52–1.02); $p = 0.064$]. Treatment-related grade ≥ 3 adverse events were higher in the alisertib/paclitaxel group: 67% versus 25%; main adverse events (all grades) were hematological and gastrointestinal. However, health-related quality of life was similar for both groups. In an exploratory analysis, patients with c-MYC expression benefited most from the combination while the opposite was found for the c-MYC-negative group. For the c-MYC-positive group, median PFS was 4.6 months for the combination and 2.3 months for paclitaxel [HR (95% CI) 0.29 (0.12–0.72)]. For the c-MYC-negative groups, median PFS was 3.3 and 5.2 months, respectively [HR (95% CI) 11.9 (1.52–91.2)] [87].

Barasertib (AZD1152), another aurora kinase inhibitor, showed promising preclinical results in SCLC [88], and only one trial is ongoing NCT01935336 (Table 2).

2.3.7. Lurbinectedin

Lurbinectedin inhibits active transcription in tumor cells and acts synergistically with doxorubicin. In a phase I trial including relapsed SCLC patients, recommended phase II dose was doxorubicin 50 mg/m² iv on day 1 of a 21-day schedule and lurbinectedin 4.0-mg flat dose iv on the same day. After reaching a cumulative dose of 450 mg/m² doxorubicin, patients were switched to lurbinectedin 7.0-mg flat dose to avoid doxorubicin cardiomyopathy. Twenty-seven SCLC patients were evaluable. Toxicity profile was manageable; grade 4 toxicities were only hematological (79% neutropenia), grade 3 toxicities were also mainly hematological, with also in a low percentage of patients liver test abnormalities, fatigue, infections, mucositis, and electrolyte disturbances. Second-line RR in platinum-sensitive disease were as high as 91.7% with a median PFS of 5.8 months; in platinum-resistant disease, RR was 33.3% with a median PFS of 3.5 months. Third-line RR was 20%, with a median PFS of 1.2 months [89]. Lurbinectedin plus doxorubicin is currently compared to cyclophosphamide/doxorubicin/vincristin or topotecan in the ATLANTIS trial (NCT02566993).

2.3.8. Stem-cell inhibitors

Hedgehog inhibitors have also been evaluated in SCLC as the Hedgehog pathway has been implicated in SCLC tumor initiation and progression. In a phase I trial ($N = 15$ newly diagnosed ED-SCLC patients), the hedgehog inhibitor sonidegib (LDE225) was combined with cisplatin/etoposide. About 800 mg sonidegib daily was the recommended phase II dose. The most common grade 3 toxicities were anemia, neutropenia, CPK elevation, nausea, and fatigue. About 79% of patients had partial responses, and one patient with SOX2 amplification (reported to drive hedgehog signaling) remained progression free on maintenance sonidegib after 27 months [90]. Currently, no trials are ongoing on clinicaltrials.gov in SCLC.

Vismodegib, another hedgehog inhibitor, was tested in a randomized phase II trial (E1508), including 152 treatment-naïve advanced SCLC patients. Patients were randomized to standard chemotherapy, or standard chemotherapy combined with vismodegib 150 mg/day orally or cixutumumab (insulin-like growth factor 1 receptor antibody). Primary end point was

PFS: the trial was negative with a HR (95% CI) for vismodegib-chemo versus chemo: 0.98 (0.65–1.47) ($p = 0.45$). The addition of vismodegib did not increase the percentage of grade ≥ 3 adverse events [91].

One more trial has completed recruitment but results are not yet available: NCT01579929, a phase I trial of the combination of LDE225, with etoposide and cisplatin as first-line treatment of ED-SCLC.

2.3.9. Angiogenesis inhibition

Several trials have attempted to incorporate an angiogenesis inhibitor in the treatment of SCLC but all failed to show an OS improvement despite sometimes an improvement in PFS.

Adding bevacizumab after response to two cycles of induction chemotherapy did not result in an improved median PFS in the IFCT 0802-phase II–III trial (NCT00930891) [92]. Based on, among others, the positive PFS results of the phase II SALUTE trial (NCT00403403, first-line chemotherapy $\pm$ bevacizumab, followed by maintenance bevacizumab or placebo) [93], the phase III GOIRC-AIFA FARM6PMFJM trial (EudraCT No. 2007-007949-13, $N = 204$) was launched, with a similar design as the SALUTE trial. The study failed its primary end point as median OS was 8.9 months for the placebo group and 9.8 months for the bevacizumab group (HR 0.78, 95% CI 0.58–1.06, $p = 0.113$). However, in a subgroup analysis, patients who received maintenance bevacizumab (43% in the EP + bevacizumab group) had a statistically significant superior OS; so, continuation of an angiogenesis inhibitor across all lines might be an option [94]. Trials with other angiogenesis inhibitors (nintedanib, thalidomide, sunitinib, vandetanib) also failed to improve OS [66,67,95,96]. Based on these results, an angiogenesis inhibitor should only be administered to SCLC patients in the context of a clinical trial. Ziv-aflibercept binds circulating VEGF and might represent a new treatment option to improve outcome in SCLC. However, when added to topotecan in a phase II trial, only PFS but not OS improved, at a cost of increased toxicity [97]. Bevacizumab added to paclitaxel, topotecan, or irinotecan also failed to improve outcome in relapsed SCLC patients [98–100].

3. Immunotherapy in SCLC

3.1. Preclinical rationale

SCLC has a high rate of somatic mutations: non-synonymous mutation rates of up to 8.6 mutations per million base pairs have been found [29,32]. They are often induced by smoking: benzo(a)pyrene (a carcinogenic compound of tobacco) and its active metabolite covalently binds to DNA, which can result in a DNA synthesis block leading to aberrant centrosome amplification. In turn, this can lead to abrogated p53 function and chromosome 3p deletion (which contains multiple tumor suppressor genes) [101–103]. This loss of tumor suppressor genes leads to increased mutagenesis. In 25% of SCLC patients, C:G $\rightarrow$ A:T transversions are found and they are an indication of heavy smoking [29,104]. Moreover, aberration of the intrinsic apoptotic pathway by inversion of the Bcl-2/Bax ratio results in further tumor growth [105]. Another signature found in SCLC which is linked to smoking and an increased mutagenesis is

the apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) signature [106].

A high tumor mutational burden (TMB) has been associated with a favorable outcome when treated with immune checkpoint inhibitors. As SCLC has a high mutational burden, this provides opportunities for the immune system to recognize and attack the tumor cells [107]. Furthermore, approximately 15–30% of SCLCs express PD-L1 [108], and PD-L1 expression is often associated with higher RR in other tumors such as NSCLC [109]. Evidence that SCLC induces an immune response can be found in the relatively high incidence of paraneoplastic syndromes neoplastic-triggered autoimmune diseases in SCLC [110]. Moreover, SCLC patients in which immune activity is shown have a better outcome. For example, a higher CD45⁺ T-cell count was associated with improved prognosis (irrespective of stage and performance status) [111]. High effector T-cell counts were more often found in LD-SCLC compared to ED-SCLC, and higher effector-to-regulatory T-cell ratios were associated with improved outcome [112,113]. Immune checkpoint inhibitors are now incorporated in the treatment strategy of advanced NSCLC, either in first line or beyond [109,114–116]. Furthermore, in the PACIFIC trial (NCT02125461) maintenance, durvalumab (anti-PD-L1 antibody) showed a PFS benefit in stage III NSCLC patients treated with concurrent CRT, compared to placebo [117]. Trial data for SCLC are discussed below.

3.2. Trial data with immunotherapy in LD-SCLC

Currently, there are only completed vaccination trials and interferon trials, but no completed checkpoint inhibitor trials in LD-SCLC. Results from trials including LD as well as ED-SCLC patients will be discussed in the LD-SCLC section. Completed trials are summarized in Table 3 and ongoing trials are summarized in Table 4.

3.2.1. Vaccination trials in LD-SCLC

So far, results with vaccination have been disappointing. In a randomized phase III trial, LD-SCLC patients responding to chemoradiation were randomized between five vaccinations of Bec2 (2.5 mg)/BCG vaccine or observation. Bec2 is an anti-idiotypic antibody that mimics GD3. GD3 is expressed on the surface of tumor cells. Primary end point was OS and 515 patients were randomized. The study was negative for its primary end point: median OS was 14.3 months for the observation arm and 16.5 months for the vaccination arm [HR (95% CI) 1.12 (0.91–1.37); $p = 0.28$] [118].

In a phase I trial ($N = 16$), vaccination of SCLC patients (LD and ED-SCLC) with a major response to their initial therapy with synthetic fucosyl GM-1 conjugated to keyhole limpet hemocyanin at different dose levels was safe and induced an IgM-antibody response. However, no radiological responses were observed [119]. Another phase I trial vaccinated SCLC patients ($N = 18$, LD and ED-SCLC) responding to initial therapy, with a polySA vaccine. PolySA is a polymer side chain bound to the neural cell adhesion molecule that is extensively expressed on the surface of SCLC cells. The vaccine was safe and antibody responses were documented but radiological

responses were not provided. Median OS was 22.9 months rather encouraging in this patient population [120].

The two ongoing vaccination trials in LD-SCLC have been terminated: NCT00776295: autologous SCT followed by dendritic cell p53 vaccination, terminated because of low accrual; NCT00045617: Chemoradiation and monoclonal antibody 11D10 or anti-idiotypic monoclonal antibody GD2 anti-idiotypic vaccine, terminated because of lack of drug availability.

3.2.2. Immunotherapy trials in LD-SCLC

Interferon (IFN) therapy has been evaluated in SCLC. IFNs have immunoregulatory, antiangiogenic, and antiproliferative effects. In a randomized phase II trial including 164 chemo-naïve SCLC patients (62 LD-SCLC), patients were randomized to chemotherapy alone (group A), or chemotherapy combined with IFN- α (group B), IFN- γ (group C), or both IFN- α and IFN- γ (group D). The trial was negative for its primary end point: median OS for group A–D was 10.0, 10.3, 8.3, and 11 months, respectively ($p > 0.05$). When compared to the other groups, median OS was significantly higher for LD-SCLC patients treated in group B: median OS for group B was 34 versus 19 months for group A ($p = 0.039$), 13.6 months for group C ($p < 0.005$), and 17 months for group D ($p = 0.038$). However, number of LD-SCLC patients per group was small [121].

3.2.3. Checkpoint inhibitors

The concept of maintenance checkpoint inhibition is currently also tested in limited-stage SCLC in several trials; these are summarized in Table 4.

3.3. Trial data with immunotherapy in ED-SCLC

3.3.1. Vaccination trials in ED-SCLC

Besides the trials that included LD-SCLC as well as ED-SCLC (summarized in the LD-SCLC section), three other vaccination trials included only ED-SCLC patients. In a single-arm phase II trial ($N = 10$ pretreated SCLC patients), a personalized peptide vaccination was tested. The antigens in the vaccine were selected based on preexisting host immunity. The vaccine was administered weekly for 6 weeks and biweekly thereafter. Four patients discontinued during the weekly vaccination due to rapid disease progression; for the other six patients, peptide-specific immunological boosting was observed. At data-lock, two patients were still alive (survival 24.5 and 10 months); survival of the other patients was 25.0, 9.5, 6.5, and 6 months [122]. A similar phase II study included 46 ED-SCLC patients (pretreated and treatment-naïve). The treatment was safe, and median OS was improved in those with increased IgG responses to a greater number of nonvaccinated peptides after the second cycle of vaccination (40.7 vs 12.6 months, $p = 0.010$) [123].

As the p53 gene is mutated in approximately 90% of SCLC, a vaccine consisting of dendritic cells transduced with the full-length wild-type p53 gene delivered via an adenoviral vector has been evaluated in ED-SCLC patients ($N = 29$). Vaccines were given at two-weekly intervals. About 57% had p53-specific T-cell responses, but only one patient responded clinically while the others progressed. Interestingly, 62% of patients responded to chemotherapy that immediately followed the

Table 3. Completed trials with immune therapies in SCLC.

Author, year	Treatment	Trial type	NSCLC	Primary study objective	Outcome
Vaccination trials					
Giaccone, 2005 [118]	Bec2/BCG vaccine or observation after response to CRT	Phase III	515 Only LD	OS	Median OS 14.3 m (observation) vs 16.5 m (vaccination) HR (95% CI) 1.12 (0.91–1.37); $p = 0.28$
Krug, 2004 [119]	Synthetic fucosyl GM-1 conjugated to keyhole limpet hemocyanin vaccine after major response to initial treatment	Phase I	16 ED and LD	Establish the lowest effective dose capable of inducing antibody production	Lowest dose 10 µg No responses
Krug, 2012 [120]	PolySA vaccine after response to initial trial	Phase I	18 ED and LD	Cf Krug 2004, also safety	Lowest dose 10 µg 6% grade 3 toxicity No responses
Terazaki, 2012 [122]	Personalized peptide vaccination	Phase II Single arm	10 ED	Immunological responses	Immunological boosting in the 6 patients that received at least one cycle (6 vaccinations)
Sakamoto, 2017 [123]	Personalized peptide vaccination	Phase II Single arm	46 ED	Feasibility	2% grade 3 toxicity 70% and 95% Peptide-specific IgG responses to the vaccinated peptides after 1 and 2 cycles, respectively
Antonia, 2006 [124]	Dendritic cells transduced with the full-length wild-type p53 gene vaccine		29 ED	Evaluate immunological and clinical effects of vaccine	57% had p53-specific T-cell responses ORR 3%
IFN-based trials					
Zarogoulidis, 2013 [121]	CT, CT + IFN-alfa or CT + IFN-gamma or CT + IFN-alfa + gamma	Phase II	164 (38% LD)	OS	Median OS 10.0, 10.3, 8.3, and 11 m, respectively ($p > 0.05$)
Pillai, 2014 [125]	Paclitaxel + IFN-alfa + 13-CRA	Phase II	37	ORR	ORR 9% Median PFS 2.0 m
Checkpoint inhibitor trials in ED-SCLC					
Reck, 2016 [126]	CT + ipilimumab or placebo	Phase III Double blind	1132 954 received study drug/placebo	OS in patients that received at least 1 dose of study drug/placebo	Median OS 11.0 m (ipilimumab) vs 10.9 m (placebo) HR 0.94, 95% CI 0.81–1.09, $p = 0.38$
Ott, 2017 [127]	Pembrolizumab in PD-L1 expressing ($\geq 1\%$) patients	Phase I	24	Safety	4% grade 5 toxicity (colitis) 4% grade 3 toxicity ORR 33%
Gadgeel, 2018 [128]	Pembrolizumab maintenance	Phase II Single arm	45	PFS from start maintenance	Median PFS 1.9 m, median OS 9.7 m ORR 11.8%
Chung, 2018 [129]	Pembrolizumab second line and beyond	Phase II Single arm	107	ORR	median PFS 1.4 m, median OS 9.4 m ORR 18.7%
Goldman, 2018 [130]	Durvalumab second line and beyond	Phase II Single arm	21	Safety ORR	ORR PD-L1 positive vs PD-L1 negative, 35.7% vs 6.0% No grade ≥ 3 toxicities ORR 9.5%
Bondarenko, 2018 [137]	Durvalumab + tremelimumab followed by durvalumab maintenance	Phase II	21	ORR	Median PFS 1.9 m, median OS 4.8 m ORR 9.5%
Antonia, 2016 [134]	Nivolumab or nivolumab + ipilimumab followed by nivolumab maintenance	Phase I/II 3-arm	216	Safety ORR	Median PFS 1.9 months Median OS 6.0 months ORR nivolumab monotherapy 10% ORR nivolumab + ipilimumab 19–33%
Pujol, 2018 [131]	Atezolizumab or standard chemotherapy	Phase II Randomized noncomparative	73	ORR	Outcomes improved in TMB-high group ORR atezolizumab 2.3% Median PFS atezolizumab 1.4 months ORR chemotherapy 10%
Horn, 2018 [133]	Carboplatin/Etoposide + atezolizumab or placebo	Phase III	403	OS	Median PFS chemotherapy 4.3 months Median OS atezolizumab 12.3 months Median OS control arm 10.3 months HR 0.70, 95% CI 0.54–0.91, $p = 0.007$
Agonistic antibodies stimulating the immune system					
Thomas, 2017 [138]	Maintenance leftolimod vs observation	Phase II Open label	102	OS	Median OS 279 days (leftolimod) vs 272 days (control) HR 1.27, 95% CI 0.80–2.01, $p = 0.53$

N: Number; SCLC: small-cell lung cancer; LD: limited disease; ED: extensive disease; BCG: Bacillus Calmette-Guérin; CT: chemotherapy; OS: overall survival; m: months; HR hazard ratio; CI confidence interval; TRT: thoracic radiotherapy; PFS: progression-free survival; IFN: interferon; 13-CRA: 13-*cis*-retinoic acid; ORR: response rate; PD-L1: programmed death-ligand 1.

Table 4. Ongoing trials with immune therapies in SCLC.

Clinical trial.gov number	Stage	Phase	Primary objective	Primary end point	Treatment	Locations	Sponsor
Vaccination + checkpoint inhibitor trials							
NCT03406715	ED	II	Activity	DCR	Ipilimumab + nivolumab + dendritic cell based p53 vaccine (Ad.p53-DC)	Lee Moffitt Cancer Center and Research Institute	BMS
NCT02688673	ED	I/II	Activity	ORR	Adenovirus-transfected autologous DC vaccine plus CIK cells	Unknown	Affiliated Hospital to Academy of Military Medical Sciences
Checkpoint inhibitor trials in LD-SCLC							
NCT02046733	LD	II	Efficacy	PFS; OS	CRT → nivolumab + ipilimumab → nivolumab	EU	ETOP
NCT02402920	LD	I	Safety	DLT	CRT + pembrolizumab → pembrolizumab	MD Anderson	MD Anderson
NCT03585998	LD	II	Efficacy	PFS	CRT + durvalumab → durvalumab	Samsung Medical Center	Samsung Medical Center
NCT03540420	LD	II	Efficacy	2yOS	CRT → avelumab vs CRT	Norway	Norwegian University of Science and Technology
NCT03509012	LD	I	Safety	DLT	<ul style="list-style-type: none"> Durvalumab + tremelimumab + CT Durvalumab + CRT Durvalumab + tremelimumab + CRT 	World	AZ
Checkpoint inhibitor first-line/maintenance ED-SCLC trials							
NCT03325816	ED	I/II	Safety	RP2D; PFS	Nivolumab + 177Lu-DOTA0-Tyr3-Octreotate	US	BMS
NCT03382561	ED	II	Efficacy	PFS	Nivolumab + CT → Nivolumab vs CT	US	NCI
NCT02538666	ED	III	Efficacy	PFS; OS	Nivolumab vs nivolumab + ipilimumab vs placebo	World	BMS
NCT02580994	ED	II	Efficacy	PFS	CT + Pembrolizumab → pembrolizumab	World	EORTC
NCT02934503	ED	I/II	Activity	Change PD-L1 expression	CT + pembrolizumab → RT	NY University	NY University
					CRT → CT + pembrolizumab		
					CT → pembrolizumab		
					CRT → pembrolizumab		
NCT03043872	ED	III	Efficacy	PFS; OS	Durvalumab + tremelimumab + CT vs CT	World	AZ
NCT02658214	ED	I	Safety	DLT	Durvalumab + tremelimumab + CT	World	AZ
NCT03568097	ED	II	Activity	1yPFS	Avelumab + CT	Greece	Hellenic Cooperative Group
NCT03066778	ED	III	Efficacy	OS	CT + atezolizumab	World	Roche
Checkpoint inhibitor second-line and beyond ED-SCLC trials							
NCT03026166	ED	I/II	Safety	DLT	Rovalpituzumab Tesirine + nivolumab/ Nivolumab + ipilimumab	World	AbbVie
NCT03575793	ED	I/II	Safety	MTD	Nivolumab + ipilimumab + plinabulin	Rutgers Cancer Institute of New Jersey	Rutgers Cancer Institute of New Jersey
NCT03253068	ED	II	Activity	ORR	Pembrolizumab + amrubicine	Wakayama Medical University	Wakayama Medical University
NCT03402880	ED	II	Activity	ORR	Pembrolizumab + epacadostat	US	City of Hope Medical Center
NCT03371979	ED	I/II	Activity	ORR	Pegzilarginase + pembrolizumab	US	Aeglea Biotherapeutics
NCT02701400	ED	II	Efficacy	PFS	Durvalumab + tremelimumab + RT	Emory University	AZ
NCT03085849	ED	I	Safety	DLT	SGL-110 → Durvalumab + tremelimumab	University	Columbia University
NCT02734004	ED	I/II	Activity	ORR	Olaparib + durvalumab	World	AZ
NCT02734004	ED	I/II	Activity	DCR	<ul style="list-style-type: none"> Olaparib + durvalumab Olaparib + durvalumab + bevacizumab 	World	AZ
NCT02937818	ED	II	Activity	ORR	<ul style="list-style-type: none"> Durvalumab + tremelimumab AZD1775 and carboplatin AZD6738 + olaparib 	EU	AZ
NCT03262454	ED	II	Activity	ORR	RT → atezolizumab	Korea	NCC Korea

ED: Extensive disease; LD: limited disease; DCR: disease control rate; ORR: objective response rate; BMS: Bristol-Myers Squibb; PFS: progression-free survival; OS: overall survival; CRT: chemoradiation; EU: European Union; ETOP: European Thoracic Oncology Platform; DLT: dose-limiting toxicity; CT: chemotherapy; AZ: AstraZeneca; RP2D: recommended phase 2 dose; US: United States; NCI: National Cancer Institute; EORTC: European Organization for Research and Treatment of Cancer; PD-L1: programmed death-Ligand 1; NY: New York; y: year; CIK: cytokine-induced killer; MT: maximum-tolerated dose; ORR: objective response rate; NCC: national cancer center.

vaccination and responses were linked to induction of immunologic response to vaccination [124].

Several other vaccination trials are ongoing (Table 4).

3.3.2. Immunotherapy trials

As described in Section 2, trials with monotherapy Bcl-2 inhibition have been disappointing. In a phase II trial, IFN- α was added to the Bcl-2-modifying agent 13-*cis*-retinoic acid (13-CRA) and paclitaxel. Primary end point was ORR. Thirty-seven relapsed ED-SCLCs were enrolled and were treated with IFN- α (6 million units/m² subcutaneously) and 13-CRA 1 mg/kg days 1 and 2, and paclitaxel 75 mg/m² iv on day 2 of each week for 6 weeks of an 8-week schedule. ORR was only 9% and PFS was only 2 months. Therefore, this combination is not further studied [125].

Checkpoint inhibitors (anti-PD-(L)1 and anti-CTLA4) have shown efficacy in SCLC in some (early phase) trials but other trials were negative. Results are summarized below.

Ipilimumab, a CTLA-4 inhibitor, did not result in an improved OS when added to platinum–etoposide in a first-line, double-blind, randomized phase III trial (NCT01450761). Primary end point was OS among patients that received at least one dose of study therapy. About 1132 treatment-naïve ED-SCLCs were randomized to platinum-doublet chemotherapy with phased ipilimumab 10 mg/kg every 3 weeks (start at cycle 3 of chemotherapy till cycle 6). A total of 954 patients received at least 1 dose of ipilimumab/placebo. The trial was negative: median OS was 11.0 months for the experimental arm and 10.9 months for the standard treatment (HR 0.94, 95% CI 0.81–1.09, $p = 0.38$). Except for diarrhea, rash, and colitis, rates and severity of treatment-related adverse-events were similar for both groups. However, treatment discontinuation occurred more often in the investigational arm (18% vs 2%) [126].

A phase I trial (KEYNOTE-028, NCT02054806) with pembrolizumab (PD-L1 inhibitor, 10 mg/kg every 2 weeks for up to 24 weeks) showed promising results in pretreated, PD-L1 expressing ($\geq 1\%$) SCLC patients ($N = 24$). ORR was 33%, median PFS was only 1.9 months but response was durable in responding patients (DOR 19.4 months). Median OS was 9.7 months. One patient had a grade 5 colitis, and another had a grade 3 bilirubin elevation. No other grade 3–5 adverse events were observed [127]. However, pembrolizumab maintenance therapy failed to improve PFS in a single-arm, phase II trial (NCT02359091) with 45 patients. Median PFS was only 1.4 months, RR was 11.8%, and median OS was 9.6 months. The small subgroup of PD-L1-positive patients ($N = 9$) had a higher PFS compared with the PD-L1-negative patients (6.5 vs 1.3 months) [128]. Pembrolizumab monotherapy (200 mg iv every 3 weeks for up to 2 years) was also evaluated in the second-line and beyond phase II basket study KEYNOTE-158. Patients were selected regardless of biomarker status. Primary end point was ORR. About 107 patients were enrolled in the SCLC cohort, and 14% was PD-L1 positive ($\geq 1\%$). ORR was 18.7% and 30% had disease control. ORR was higher in the PD-L1 positive cohort ($N = 42$) compared to the PD-L1 negative cohort ($N = 50$) and was 35.7% vs 6.0%. Median DOR was not reached; median PFS was 2.0 months and was similar for both PD-L1 status cohorts. Median OS was higher for the

PD-L1-positive cohort and was 14.9 vs 5.9 months. About 13% had grade 3–4 treatment-related adverse events [129].

Durvalumab monotherapy (10 mg/kg iv every 2 weeks for up to 12 months) has also been evaluated in a phase I/II trial including a cohort of relapsed, unselected SCLC patients ($N = 21$). ORR was only 9.5%; median PFS was 1.5 months with a median OS of 4.8 months. However, DOR for the two responding patients was 14.6 and 29.5+ months. No new safety signals were observed [130]. Last, atezolizumab monotherapy (1200 mg iv every 3 weeks) has been compared to standard chemotherapy as second-line treatment for ED-SCLC in the randomized, noncomparative phase II IFCT-1603 trial ($N = 73$). For atezolizumab, ORR was 2.3% with a median PFS of 1.4 months. For chemotherapy, ORR was 10% with a median PFS of 4.3 months [131].

It is possible that the limited tumor expression of PD-L1 combined with an exhausted immune cell phenotype contributes to the limited activity of monotherapy checkpoint inhibition [132]. The combination of PD-L1 inhibition with chemotherapy or CTLA-4 inhibition is more promising in SCLC. The combination of PD-L1 inhibition with chemotherapy improved OS of treatment-naïve ED-SCLC ($N = 403$) in the randomized phase III IMpower 133 trial. Patients were randomized between carboplatin/etoposide/atezolizumab followed by maintenance atezolizumab or carboplatin/etoposide/placebo followed by maintenance placebo. Atezolizumab was given at a flat dose of 1200 mg every 3 weeks. Median OS was 12.3 months for the atezolizumab arm and 10.3 months for the control arm (HR 0.70, 95% CI 0.54–0.91, $p = 0.007$). Compared to previous safety findings of the individual agents, no new safety signals were observed with the combination [133]. The phase III KEYNOTE 604 trial (NCT03066778) with a similar design as the IMpower133 (pembrolizumab 200 mg flat dose instead of atezolizumab) is currently enrolling patients.

Data with PD-L1 and CTLA-4 inhibition combined are also interesting. For example, in the non-randomized phase I/II CHECKMATE-032 trial (NCT01928394) including relapsed SCLC patients ($N = 216$), RR with monotherapy nivolumab (3 mg/kg every 2 weeks) was 10%, but RR with nivolumab plus ipilimumab (1 plus 1 mg/kg, 1 plus 3 mg/kg, or 3 plus 1 mg/kg iv every 3 weeks for 4 cycles followed by nivolumab monotherapy 3 mg/kg every 2 weeks) ranged from 19% to 33%. Responses were in both groups durable; median DOR was 14.2–17.9 months. PD-L1 expression was not associated with response [134]. In the randomized expansion cohort of this trial, similar results were obtained. Grade 3–4 adverse events were higher with the combination therapy [135]. In an exploratory analysis of this trial, 211 patients (53%) were evaluable for TMB (measured with whole exome sequencing) and patients were divided in tertiles according to TMB value. Outcomes in the TMB-evaluable population were similar compared with the intention-to-treat population. ORR for high TMB patients compared to low/medium TMB patients was higher in the nivolumab monotherapy group and in the nivolumab/ipilimumab group (21.3% vs 4.8–6.8% and 46.2% vs 22.2–16.0%, respectively). For nivolumab monotherapy, median PFS was similar across the TMB tertiles (1.3, 1.3, and 1.4 months). However, for nivolumab/ipilimumab, median PFS was higher for the TMB-high group compared with the

TMB low/medium groups (7.8 vs 1.5–1.3 months). Median OS was also higher for the nivolumab/ipilimumab TMB-high group: 22.0 vs 3.4–3.6 months [136]. In the phase II BALTIC trial (cohort A), durvalumab 1500 mg iv and tremelimumab 75 mg iv every 4 weeks for up to 4 months, followed by maintenance durvalumab 1500 mg iv every 4 weeks were evaluated in platinum-refractory/resistant ED-SCLC ($N = 21$). ORR was 9.5% with a median PFS of 1.9 months and a median OS of 6.0 months. Twelve-month OS was 32.7%. Grade ≥ 3 treatment-related AEs occurred in 9.5%, including one fatal hemorrhagic enterocolitis [137].

PD-L1 and CTLA-4 inhibitors combined with chemotherapy are currently being tested in the phase III CASPIAN trial (NCT03043872, platinum/etoposide vs durvalumab/platinum/etoposide vs durvalumab/tremelimumab/platinum/etoposide).

Furthermore, multiple other checkpoint inhibitor trials are ongoing in SCLC and are summarized in Table 4.

Agonistic antibodies are another method of stimulating the immune system. Leflotolimod, a TLR9 agonist, targets TLR9 positive cells and activates both the innate and adaptive immune system. In subgroup analyses of a maintenance randomized phase II trial (NCT02200081) including SCLC patients who responded to first-line platinum-doublet chemotherapy, interesting results were found. Median OS was not significantly different for the total study population ($N = 102$, 279 days for lefotolimod, 272 days for the control arm, HR 1.27, 95% CI 0.80–2.01, $p = 0.53$), but results were promising although not significantly different in the predefined subgroup of COPD patients (median OS 316 vs 246 days, HR 0.54, 95% CI 0.21–1.38). Promising results were also found in the predefined subgroup of patients with baseline low number of activated B cells (median OS 284 vs 231 days, HR 0.59, 95% CI 0.29–1.21) [138].

4. Conclusion

SCLC is a tumor with a poor prognosis, mainly diagnosed in an advanced stage as screening is not effective due to its high aggressiveness. Smoking cessation is the best method to prevent SCLC development.

Despite aggressive treatment of early and locally advanced disease, SCLC often relapses. First-line chemotherapy provides good RRs in advanced disease, but PFS and OS are limited. Targetable molecular aberrations are very rare in SCLC and almost all attempts made so far have been unsuccessful, although Rova-T and anlotinib are more promising. New drugs such as immune checkpoint inhibition are promising in SCLC, especially in combination with chemotherapy, but still more data and better predictive markers are needed.

5. Expert commentary

The prognosis of most SCLC patients is still poor, despite the steps forward in SCLC molecular characterization, and the (small) improvements in systemic treatment.

The lack of identification of clear prognostic and predictive biomarkers has limited the advances in treatment efficacy. This has most likely determined the failure in the development of

most compounds tested so far. One of the reasons that might have contributed is the absence of an adequate amount of tissue material for analysis, since the diagnosis is mostly by cytology. On the other hand, the complex tumor biology with the co-activation of several pathways and the rapid development of resistance is also a challenge. Moreover, tumor heterogeneity, not yet well studied for this particular lung cancer type, could play a key role in this disease and this needs to be further explored.

In this scenario, liquid biopsy could represent a solution to hopefully provide further data to better characterize and monitor this disease.

Due to its highly mutational profile and rapid growth pattern, immunotherapy combinations could be another step forward in SCLC treatment. The phase III IMpower133 study combining atezolizumab with carboplatin and etoposide is the first phase III trial in about 20 years reporting a significant improvement (although modest) in OS [133]. Multiple other combination trials are ongoing, but the main research focus should be defining which patients benefit most from a specific combination therapy (e.g. PD-(L)1 inhibition combined with chemotherapy, PD-(L)1 and CTLA4 combinations with or without chemotherapy, and other combinations). Particularly, toxicity should also be thoroughly evaluated.

Other challenges will be, both for LD and ED-SCLC, the identification of the best treatment sequence and the evaluation of the potential efficacy of rechallenging immunotherapy. Academic trials could represent the best way to test the sequential strategy in order to finally provide clinicians the support needed to treat patients in every-day clinic. The ultimate goal is to prolong OS, and maintain/improve quality of life, without a too high financial toxicity.

Crucial fields in the next future will also certainly be the control of paraneoplastic syndromes, quite frequent in these patients [110], as well as the control and treatment of brain metastases [139], very frequently present already at diagnosis, but also often a site of disease progression. Unfortunately, SCLC patients with brain metastases are underrepresented in clinical trials (e.g. only 8.5% brain metastases in the atezolizumab arm of the IMpower133 study) [133].

The achievements made so far with targeted agents are small, and most of the compounds tested did not shown any benefit in activity or efficacy [28,70]. More promising are combinations with DLL3-antibodies or PARPi that could potentially overcome mechanisms of resistance resulting hopefully in a meaningful clinical benefit.

The results of antiangiogenic drugs have been rather disappointing so far, but potential combinations with targeted agents and/or immunotherapy are currently tested in clinical trials, and results should be awaited before cutting off the development of these compounds in this tumor type. Hopefully the improved treatments in ED-SCLC also translate to improved survival in LD-SCLC when tested in this setting.

6. Five-year view

In the coming years, we expect the focus of clinical research to be on (1) predictive factors for immunotherapy, (2) the identification of mechanisms of resistance to immunotherapy and

how to overcome them, and (3) the best treatment sequence strategies.

Moreover, preclinical and clinical research should focus on better understanding the crosstalk signaling pathways so as to finally manage targeted agents correctly.

Key issues

- SCLC patients usually have a small amount of tissue to be analyzed, limiting therefore translational research
- There is a clear lack of prognostic and predictive biomarkers in this rapidly evolving disease
- Targeted therapies have failed to improve outcome, although newer therapies such as PARPi and DLL3-antibodies are promising
- Immunotherapy combinations can improve long-term outcome in SCLC, but better predictive markers need to be identified so to develop the best treatment strategy and sequence

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