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Challenges in the treatment of small cell lung cancer in the era of immunotherapy and molecular classification

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Original Citation:

Challenges in the treatment of small cell lung cancer in the era of immunotherapy and molecular classification / Caliman, Enrico; Fancelli, Sara; Petroni, Giulia; Gatta Michelet, Marta Rita; Cosso, Federica; Ottanelli, Carlotta; Mazzoni, Francesca; Voltolini, Luca; Pillozzi, Serena; Antonuzzo, Lorenzo. - In: LUNG CANCER. - ISSN 0169-5002. - STAMPA. - 175:(2023), pp. 88-100. [10.1016/j.lungcan.2022.11.014]

Availability:

This version is available at: 2158/1296439 since: 2023-01-23T22:20:57Z

Published version:

DOI: 10.1016/j.lungcan.2022.11.014

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Journal Pre-proofs

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PII: S0169-5002(22)00687-0
DOI: <https://doi.org/10.1016/j.lungcan.2022.11.014>
Reference: LUNG 7095

To appear in: *Lung Cancer*

Received Date: 31 August 2022
Revised Date: 18 November 2022
Accepted Date: 20 November 2022

Please cite this article as: E. Caliman, S. Fancelli, G. Petroni, M.R.G. Michelet, F. Cosso, C. Ottanelli, F. Mazzoni, L. Voltolini, S. Pillozzi, L. Antonuzzo, Challenges in the treatment of small cell lung cancer in the era of immunotherapy and molecular classification, *Lung Cancer* (2022), doi: <https://doi.org/10.1016/j.lungcan.2022.11.014>

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Title: Challenges in the treatment of small cell lung cancer in the era of immunotherapy and molecular classification

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Abstract

For many years the standard of care for small cell lung cancer (SCLC) has remained unchanged. Despite decades of active research, current treatment options are limited and the prognosis of patients with extended disease (ED) SCLC remains poor. The introduction of immune checkpoint inhibitors (ICIs) represents an exception and the only recent approval for ED-SCLC. However, the magnitude of benefit obtained with immunotherapy in SCLC is much more modest than that observed in other malignancies. Different pro-immunogenic or immunosuppressive features within the tumor microenvironment of SCLC may either modulate the sensitivity to immunotherapy or conversely dampen the efficacy of ICIs. Beside immunotherapy, a deeper understanding of the molecular biology of SCLC has led to the identification of new therapeutic targets for this lethal malignancy. Recent epigenetic and gene expression studies have resulted into a new molecular classification of four distinct subtypes of SCLC, defined by the relative expression of key transcription regulators and each characterized by specific therapeutic vulnerabilities. This review discusses the rationale for immunotherapy in SCLC and summarizes the main ICIs-trials in this tumor. We provide also an overview of new potential therapeutic opportunities and their integration with the new molecular classification of SCLC.

Keywords: Small cell lung cancer; immunotherapy; molecular classification; SCLC subtypes; therapeutic strategies

1. Introduction

Small cell lung cancer (SCLC), accounting for approximately 10-20% of all lung tumor, is a deadly malignancy with a dismal prognosis and a poor 5-years survival rate [1,2]. Patients with SCLC typically present with extended disease (ED) at diagnosis. Although an initial good response to the frontline treatment is often observed, most patients rapidly develop drug resistance and suffer a rapid disease relapse within a few months. In the last decade, comprehensive genomic profiling of SCLC has highlighted the complexity of the genetic mutational landscape of this tumor [3–5], as well as other somatic mutations on transcription factors and receptor tyrosine kinases genes and epigenetic changes in chromatin modifiers enzymes [6,7]. However, although a number of potentially actionable mutations have been identified to date, no targeted therapies have been approved for SCLC. More recently, epigenetic and gene expression studies on preclinical models and on primary human tumors have resulted into a new molecular classification of four distinct SCLC subtypes. Molecular subtypes were defined by the relative expression of key transcription regulators that are responsible for neuroendocrine (achaete-scute homologue 1 [ASCL1] and neurogenic differentiation factor 1 [NEUROD1]) or non-neuroendocrine (POU class 2 homeobox 3 [POU2F3] and yes associated protein 1 [YAP1]) differentiation programs, and named SCLC-A, SCLC-N, SCLC-P and SCLC-Y, respectively [8]. In the past years, a new subtype of inflamed SCLC (SCLC-I), characterized by the expression of multiple markers of immune cell infiltration and epithelial-mesenchymal transition (EMT), has been described [9,10]. The new classification proposed by Gay et al. included the SCLC-A, SCLC-N, SCLC-P and SCLC-I tumors, each characterized by unique molecular features and specific therapeutic vulnerabilities. The SCLC-Y subgroup was not included as it resulted to be non-specific to a single biological sub-group [9,11,12].

Despite active research in the field of new therapeutic opportunities for SCLC, over the last three decades systemic therapy has not changed substantially. An exception was the introduction of immune checkpoint inhibitors (ICIs), which has set a new benchmark in clinical practice for patients with ED-SCLC [13,14]. However, available treatment options for SCLC remain still limited. A deeper knowledge of molecular aberrations in SCLC could provide the identification of new therapeutic targets and could be crucial to translate new insights into the biology of SCLC into clinical trials of molecularly driven treatments [6,15–17]. This review focuses on treatment

strategies available for ED-SCLC. We discuss the rationale for the use of immunotherapy in SCLC and provide an overview of the main trials that have evaluated ICIs in this tumor. Furthermore, we also describe other potential therapeutic options that have been the subject of recent studies and their integration with the new classification of SCLC into molecular subtypes.

2. Rationale and challenges of immunotherapy in SCLC

SCLC has been long considered an immunogenic tumor for several reasons [18,19]. Firstly, the occurrence of immune-mediated paraneoplastic syndromes (Lambert-Eaton myasthenic syndrome, encephalomyelitis and other neurological paraneoplastic disorders) reported in approximately 15-20% of SCLC patients, has been linked to autoimmune responses against antigens (e.g., HuD, HuC, and Hel-N1) expressed both by SCLC cells and healthy neurons [20,21]. Importantly, the autoimmune responses against the nervous system have also been correlated to an increased antitumor activity against tumor cells and increased tumor-infiltrating lymphocytes (TILs). This results in better outcomes for patients with both clinical evidence of paraneoplastic disorders and/or with circulating anti-neuronal nuclear antibodies [22–25]. Secondly, SCLC is characterized by an elevated tumor mutational burden (TMB), which is strongly related to the carcinogenic action of heavy tobacco exposure [26,27], and the consequent exposure of a high number of potentially immunogenic neoantigens. Several data have shown an association between high TMB and improved sensitivity to ICIs, linked to the promotion of tumor neoantigens-specific CD8+ T-cell responses [28–32]. However, despite the high prevalence of paraneoplastic disorders among SCLC patients and the high TMB, SCLC tumors are generally defined as "immune-cold" tumors. This is mainly due to the limited infiltration of immune cells into the tumor microenvironment (TME), the reduced PD-L1 expression and the lack of antigen presentation, which somewhat dampen the efficacy of immunotherapy in SCLC [19,20,33,34] (**Figure 1**).

2.1 Role of tumor microenvironment

Studies have reported a lower ratio of suppressive immune cells (such as monocytes, regulatory T (T-reg) cells and macrophages) to CD3+ lymphocytes in SCLC of long-term survivors [34,35], as well as a lower infiltration by B cells, CD3+ and CD8+ lymphocytes, compared to NSCLC tumors [36]. On the other hand, high levels of tumor-infiltrating T-reg cells and circulating myeloid-derived suppressor cells (MDSCs), that can inhibit activation, expansion and functions of effector T-cells, correlate negatively with clinical outcomes in SCLC patients [34,37,38].

Recently, different SCLC subtypes with different sensitivity to immunotherapy and chemotherapy have been identified [8,9], suggesting a subtype-dependent heterogeneity in term of immunogenicity and further complicating this scenario. In detail, the SCLC-I subtype exhibits the greatest benefit from ICIs compared to other non-inflamed subtypes. SCLC-I is characterized by a higher infiltration of cytotoxic T-cells, NK-cells and macrophages, an elevated TMB, a higher expression of checkpoint molecules (including PD-L1 and CTLA-4), and the upregulation of IFN signatures [9]. Contrarily, the immunohistochemistry analysis highlighted an immune-cold phenotype for NE-high SCLC, characterized by a decreased infiltration of CD8+ T-cells, a lower expressions of the emerging immune checkpoints indoleamine 2,3-dioxygenase (IDO) and poliovirus receptor (PVR), and of the T-cell exhaustion marker (T-cell immunoglobulin and mucin domain-3, TIM3) [39,40]. Finally, a deeper characterization of the TME of SCLC-N tumors, that are reportedly less responsive to ICIs [9], has shown an increased infiltration by exhausted CD8+ T-cells, linked to the accumulation T-reg cells and profibrotic immunosuppressive macrophages [41], as well as to a reduced NK-cell infiltration [42]. The latter effect has been proposed to be a consequence of the downregulated expression of the NK stimulatory ligand NKG2DL by SCLC tumors [43]. Interestingly, the stimulation of NK-cell activity through the activation of IL-15 signaling pathway [42] or the restoration of NKG2DL expression [43] successfully reduced metastasis dissemination and improved the efficacy of anti-PD1 antibodies in preclinical models of SCLC, thus identifying novel potential target to inflame the TME of ICI-refractory SCLC tumors.

2.2 Low PD-L1 expression

Although in several studies the PD-L1 expression has been correlated with favorable clinical outcomes for SCLC patients [44–48], others have suggested a lack of correlation between ICI efficacy and PD-L1 status [31,32,49]. This discrepancy is likely due to technical limitations, such as different detection methods (e.g., IHC, flow cytometry, mRNA expression), specificity and sensitivity of staining antibodies, definition of cut-off levels used and types of tissue biopsy analyzed [30,36]. However, most of studies suggest a relatively low expression of PD-L1 [36,50–53] with a higher proportion of PD-L1-positive SCLC among early (I-III) stages compared to ED-SCLC [54]. Moreover, a higher expression of PD-L1 was found on tumor-infiltrating immune cells rather than in tumor cells [45,55,56]. Consequently, PD-L1 cannot be considered a reliable clinical predictive marker of ICI efficacy in SCLC. Other checkpoint molecules are emerging as potential predictive biomarkers for SCLC and actionable targets to improve response to ICIs. A higher expression of B7-H3, a B7-family ligand that has been reported to mediate several pro-tumorigenic and immunosuppressive functions [36,57], has been described in SCLC specimens and correlated to a reduced intra-tumoral infiltration of lymphocytes. In addition, the CD47 “don’t eat me” signal, which reportedly inhibits macrophage and monocyte activities [58] was found to be highly expressed on the surface of SCLC cells and its blockage significantly enhanced the phagocytosis of SCLC cells in vitro and in mouse xenograft models [59]. These data, although they need to be confirmed in larger cohorts of patients, provide scientific bases for further evaluation of B7-H3- and CD47-blocking antibodies in patients with SCLC.

2.3 Lack of antigen presentation

Another immune escape mechanism is the downregulation of the expression of MHC class I and II molecules and the consequent decreased in antigen presentation. In particular, SCLC shows a low intrinsic expression of MHC class I molecules, such as HLA-A, HLA-B, HLA-C and β 2-microglobulin, as well as of several genes involved in MHC-I-mediated antigen presentation, which result in reduced presentation of neoepitopes to CD8⁺ T-cells and recognition of tumor neoantigens by cytotoxic T-cells [60–62]. Moreover, a significantly lower expression of MHC class II molecules has been detected in SCLC cell lines and tumor samples than in NSCLC, probably due to the lack of MHC class II transactivator (CIITA) [63,64]. More recently, it has been shown that the transition to a non-neuroendocrine cell state in SCLC results in the depression of MHC class I-mediated antigen presentation, which in turn promotes the recruitment of antigen-specific CD8⁺ T-cells and rejection of murine SCLC tumors [65]. Mechanistically, it has been proposed that defects in the antigen presentation machinery in SCLC tumors are a consequence of epigenetic programs. The expression of MHC class I molecules, as well as the T-cell-mediated killing of tumor cells, can be restored in NE SCLC cell lines through the pharmacological inhibition of the chromatin remodeling regulator Enhancer of zeste homologue 2 (EZH2) [62,65], thus identifying a novel actionable target to potentially increase the intrinsic immunogenicity of SCLC and improve response to ICIs.

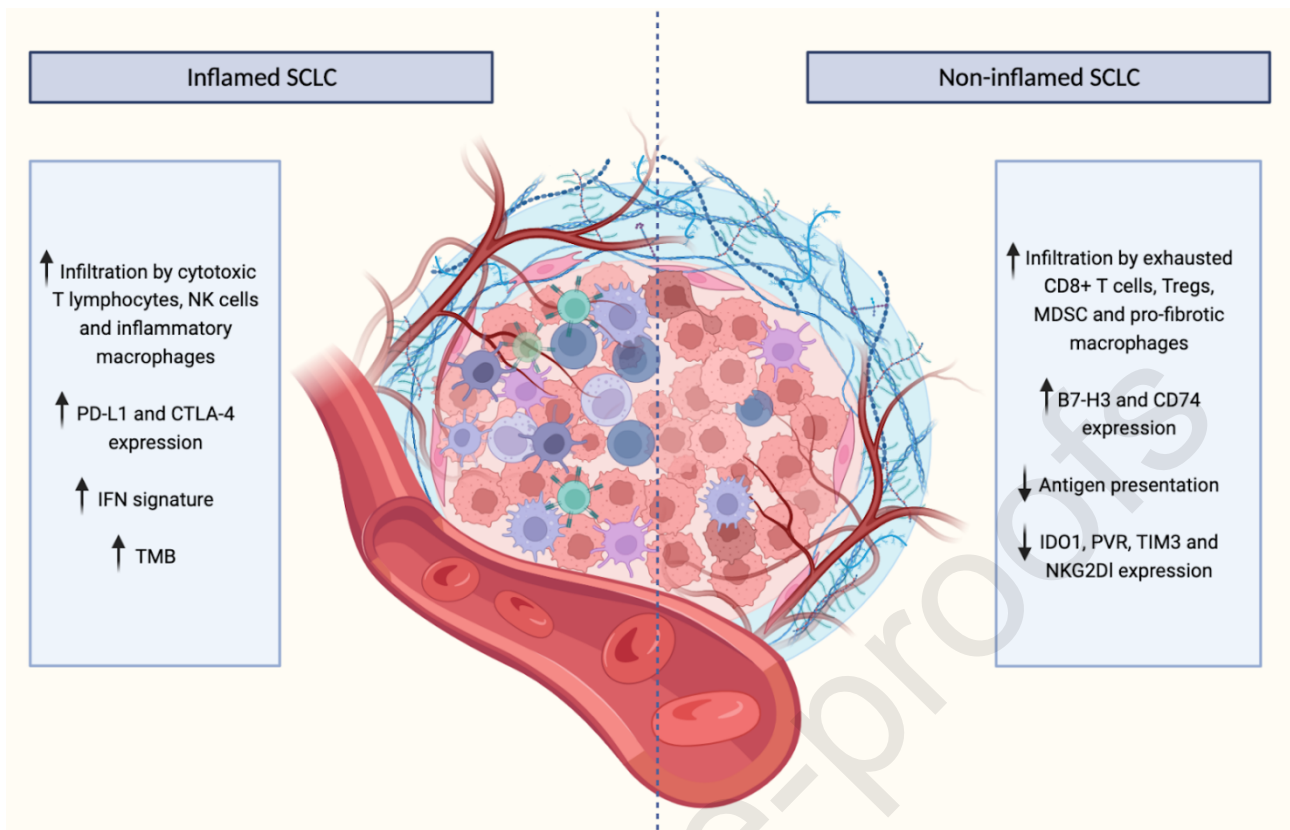


Figure 1. Features of SCLC predisposing response or resistance to immunotherapy treatment. The different cellular infiltration and characteristics of the tumor microenvironment in SCLC modulate the sensitivity to immunotherapy and can divide SCLC into 'inflamed' or 'non-inflamed' phenotypes according to its immunogenicity. The inflamed subtype is mainly characterized by the infiltration of cytotoxic lymphocytes, increased expression of checkpoint molecules (such as PD-L1 and CTLA-4), elevated tumor mutational burden (TMB) and upregulation of IFN signatures. Contrarily, in the non-inflamed phenotype a higher infiltration of suppressive immune-cells (such as exhausted CD8+ lymphocytes, T-reg cells and myeloid-derived suppressor cells) and a higher expression of B7-H3 and CD47 are found. Furthermore immune-cold SCLC exhibits a downregulation of the expression of MHC class I and II molecules, resulting in reduced antigen presentation, and a lower expression of emerging immune checkpoints. (i.e. indoleamine 2,3-dioxygenase (IDO), poliovirus receptor (PVR), T-cell exhaustion marker T-cell immunoglobulin and mucin domain-3 (TIM3) and the NK stimulatory ligand NKG2DL).

2.4 Potential approaches to enhance SCLC immunogenicity and improve ICI efficacy

Several preclinical and clinical data showed that conventional chemotherapy (CT), radiotherapy (RT) and numerous targeted agents (TAs) exert a variety of immunomodulatory effects that boost antitumor immune responses [66–68]. Thus, standard-of-care CT and RT, as well as certain TAs under clinical investigation, could be exploited to convert the “immune-cold” phenotype of SCLC into an “immune-hot” phenotype and potentially improve response to ICIs. Supporting this hypothesis, several immunomodulatory effects have been ascribed to the above anticancer treatments. In brief, CT and RT are able to reshape the TME mainly (but not only) by eliciting a form of regulated cell death in cancer cells, so called immunogenic cell death (ICD). The ICD leads to the release of tumor-specific neoantigens and damage-associated molecular patterns (DAMPs) molecules, as well as to the secretion of type I IFN, in turn enhancing MHC class I- and DC-mediated presentation of tumor antigens to cytotoxic CD8+ T-cells [66,68]. According to these notions, chemo-radiotherapy (CRT) has been recently reported to increase the levels of circulating CD8+ T-cells in patients with limited disease (LD) SCLC [69]. On the other hand, both CT and RT increase PD-L1 expression in tumor cells, thus exerting a negative immunomodulatory effect, that however can be counteracted by PD1/PD-L1 inhibitors [66,68,70]. Similar to CT and RT, various

TAs have demonstrated the ability to stimulate antitumor immune responses and to improve ICI efficacy [67]. As some examples, pharmacological inhibition of DNA damage response (DDR) with inhibitors of poly-(ADP)-ribose polymerase (PARP-I; i.e. olaparib) or checkpoint kinase 1 (CHEK1, best known as CHK1; i.e., prexasertib) enhances PD-L1 expression on cancer cells, while concomitantly induces the recruitment and activation of cytotoxic CD8+ T-cells in SCLC tumor, thus reducing tumor growth and synergizing with anti-PD-L1 antibodies [71]. Comparable findings have been also described for a bispecific antibody targeting Delta-like ligand 3 (DDL3; a Notch pathway inhibitory ligand) and T-cells [72], and a selective inhibitor of cycle dependent kinase 7 (CDK7; a key regulator of cell cycle and transcription) [73]. Along similar lines, SCLC patients that received transient treatment with the CDK4/6 inhibitor trilaciclib during CT showed increased peripheral lymphocyte cell counts and enhanced T-cell activation. Based on these promising findings several clinical trials are investigating the efficacy of ICIs as single agents and in combination with CT or TAs in patients with SCLC.

3. Principal trials of Immunotherapy in SCLC

3.1 ICIs monotherapy in pre-treated SCLC patients

Several ICIs have been evaluated in patients with recurrent SCLC. Despite some encouraging results, immunotherapy alone does not offer significant outcomes advantage over CT in this setting. The phase 1-2 trial Checkmate 032 evaluated nivolumab with or without ipilimumab in pretreated SCLC patients [49]. The combination therapy showed a better objective response rate (ORR) (22% vs 12%) and longer progression free survival (PFS) (30% vs 18%) and overall survival (OS) (40% vs 27%) than single agent nivolumab. Updated results confirmed higher ORR for the combination arm regardless of PD-L1 status, whereas median OS (mOS) resulted similar among two groups [74]. In the phase 3 Checkmate 331 trial, recurrent SCLC patients were randomized to nivolumab or CT (topotecan or amrubicin). Although the trial reported no statistical improvement for OS, a delayed separation between survival curves was described, suggesting a potential activity for nivolumab in the platinum-resistant subgroup [75]. Nivolumab plus ipilimumab were also tested as maintenance strategy after CT response. In a phase 3 randomized trial, patients who did not progress to platinum-based CT were assigned to nivolumab with or without ipilimumab or placebo. In both treated groups mOS was not significantly prolonged versus placebo [76].

The efficacy and safety of the anti-PD1 pembrolizumab was assessed for patients with ED-SCLC after failure of first line CT. In the phase Ib Keynote-028 study, pembrolizumab was administered up to 24 months in twenty-four SCLC and PD-L1-positive patients. ORR was 33.3%, compared to historical response rates of 7% to 24% for CT [77,78] and median duration of responses (DOR) was 19.4 months [48]. The phase 2 Keynote-158 study evaluated pembrolizumab for two years in recurrent ED-SCLC. ORR was 18.7% in the overall population and resulted higher in PD-L1-positive compared to PD-L1-negative patients (35.7% vs 6.0%, respectively) [47]. The update pooled analysis of the two aforementioned trials showed an ORR of 19.3%. Of note, 14 of 16 patients (88%) with a response were PD-L1-positive and 61% of responders maintained a lasting benefit for 18 months or longer [79]. Based on these results, in June 2019 the FDA granted accelerated approval to pembrolizumab for patients with recurrent SCLC who experienced progression during or after platinum-based CT and at least one other prior line of therapy.

The anti-PD-L1 durvalumab showed potential activity in 21 platinum-refractory patients with ED-SCLC in the expansion cohort of a phase 1-2 trial. Response rate was 9.5%, mPFS was 1.5 months and mOS was 4.8 months, respectively [80]. In the phase 2 BALTIC study, durvalumab was evaluated in combination with the CTLA-4 inhibitor tremelimumab in 21 pretreated ED-SCLC patients: ORR was 9.5% and the disease control rate (DCR) at 3 months was 38.1% [81].

The anti-tumor activity of the anti PD-L1 atezolizumab as single-agent in recurrent ED-SCLC was assessed in a phase 2 randomized non-comparative trial, in which 73 patients were randomized to receive either atezolizumab or CT, regardless the PD-L1 expression. Atezolizumab failed to show

significant efficacy: ORR resulted 2.3% and 10% in atezolizumab and CT group, respectively; mPFS was 1.4 months for atezolizumab and 4.3 months for CT, while no difference for OS was found [82].

3.2 ICIs plus CT in first line setting

The anti-CTLA-4 ipilimumab was the first ICI evaluated as frontline therapy for ED-SCLC. In combination with carboplatin and etoposide, ipilimumab showed an encouraging ORR of 72.4%, a one-years PFS of 15.8% and a mOS of 17 months [83]. It was also investigated in association with paclitaxel and carboplatin in a randomized phase 2 trial, in which 130 CT-naïve patients were randomized to receive paclitaxel plus carboplatin with either placebo or ipilimumab administered in two alternative regimens: concurrently with CT (concurrent-ipilimumab) or after two doses of CT (phased-ipilimumab). No improvements in OS and PFS were reported with the combination strategy, however, immune-related (ir) PFS was improved in phased-ipilimumab regimen compared with control (median irPFS 6.4 months vs 5.3 months; HR: 0.64, $p=0.03$) [84]. Finally, also a randomized double-blind phase 3 trial of ipilimumab plus platinum-etoposide for newly diagnosed-SCLC patients did not report an improvement in OS for the experimental arm [85].

Three randomized clinical trials [13,14,86] demonstrated the efficacy of anti-PD1/PD-L1 antibodies in combination with CT in treatment-naïve patients with ED-SCLC. The double-blind, placebo-controlled, phase 3 IMpower133 trial randomized 403 patients to receive the standard front-line CT with carboplatin and etoposide plus either atezolizumab or placebo for four cycles, followed by a maintenance phase until progression or unacceptable toxicity. The trial showed a significant longer OS and PFS for the experimental arm (mOS 12.3 vs 10.3 months in the atezolizumab and placebo group, respectively, HR: 0.70, 95% CI, 0.54-0.91; $p=0.007$; mPFS 5.2 vs 4.3 months, HR: 0.77, 95% CI, 0.62-0.96; $p=0.02$). The TMB subgroup exploratory blood-based analysis showed a consistent benefit in terms of OS and PFS regardless of the prespecified cutoffs of 10 or 16 mutations per megabase [13,56]. Interestingly, a subtype-specific analysis performed by Gay et al. reported that the SCLC-I subtype represents the 18.5% of all tumors in the trial and the efficacy of the addition of ICI was relevant especially in this molecular subgroup [9]. The CASPIAN trial assessed durvalumab, with or without tremelimumab, in association with standard platinum-based CT. This randomized, open-label, phase 3 study assigned 805 patients in 1:1:1 ratio to receive durvalumab/tremelimumab plus CT or durvalumab plus CT or CT alone. In the planned interim analysis, durvalumab plus CT was found to significantly improve mOS compared to the CT group (13.0 vs 10.3 months, HR: 0.73, 95% CI 0.59-0.91, $p=0.0047$) across all prespecified patient subgroups. However, the addition of tremelimumab to durvalumab did not significantly improve survival outcomes compared to control group (mOS 10.4 vs 10.5 months in the experimental and control arm, respectively; HR: 0.82, 95% CI 0.68-1.00, $p=0.0451$) [14,87]. Results from IMpower133 and CASPIAN studies led to regulatory agencies' approval of both CT and immunotherapy combinations as new 'gold standard' first-line treatments in ED-SCLC.

The phase 3 Keynote 604 trial compared pembrolizumab or placebo in association with platinum-etoposide in patients with untreated ED-SCLC. Combination treatment significantly improved PFS (HR: 0.75, 95% CI 0.61-0.91, $p=0.0023$), whereas the significance threshold for OS improvement was not met (HR: 0.80, 95% CI 0.64-0.98, $p=0.0164$) [86]. Pembrolizumab was also investigated as a two years-maintenance therapy in patients with a response or stable disease after CT induction. Although pembrolizumab did not show significant improvement in survival outcomes, patients with high PD-L1 expression obtained a clinical benefit from ICI treatment (1-year PFS and OS rates 13% and 37%, respectively) [46]. In the same maintenance setting, nivolumab was investigated in a phase 3 trial, in which SCLC patients who did not experience progression after CT, were randomized to receive nivolumab with or without ipilimumab or placebo for up to two years. The study was formally negative, as mOS was not significantly prolonged nor by ICIs combination neither by nivolumab monotherapy. However, a modest benefit in PFS was observed in the experimental groups and a trend toward OS benefit with nivolumab plus ipilimumab was

observed in patients with TMB \geq 13 mut/Mb [88].

3.3 Other on-going trials of ICIs for SCLC

Several studies are currently investigating ICIs alone or in combination with CT or other agents. Furthermore, it has been widely reported that RT exerts an immunomodulatory effect that may potentially enhance the response to ICIs [68]. While RT for ED-SCLC was historically reserved for palliation, in the era of chemo-immunotherapy the role of consolidative thoracic RT for patients with ED-SCLC is the subject of several trials [89,90]. A summary of principal ongoing studies evaluating different immunotherapy regimens both in ED- and LD-SCLC, as neo-/adjuvant therapy and in upfront, maintenance or refractory settings are summarized in the table below. In addition, the table shows the main active clinical trials of ICI therapy combined with consolidative thoracic RT for ED-SCLC.

Trial	Phase	Setting	Stage	Enrolled pts	Treatment regimen	Primary endpoints
ADRIATIC (NCT03703297)	III	consolidation after CRT	Limited	730	durvalumab vs durvalumab + tremelimumab vs placebo	PFS; OS
STIMULI (NCT02046733) [91]	II	consolidation after CRT	Limited	153	nivolumab + ipilimumab vs placebo	PFS (not- reached); OS
ACHILES (NCT03540420)	II	consolidation after CRT	Limited	212	atezolizumab vs observation	OS
LU005 (NCT03811002)	II/III	concomitant with CRT	Limited	506	atezolizumab + CRT vs placebo + CRT	OS
NCT04696939	II	neoadjuvant	Limited	100	atezolizumab + platinum/etoposide + surgery	DFS
REACTION (NCT02580994) [92]	II	I line	Extended	125	pembrolizumab + platinum/etoposide vs platinum/etoposide	PFS (not- reached)
CeLEBrATE (NCT04730999)	II	I line	Extended	52	atezolizumab + bevacizumab + carboplatin/etoposide	OS
SKYSCRAPER 02 (NCT04256421) [93]	III	I line	Extended	590	atezolizumab + tiragolumab + carboplatin/etoposide vs atezolizumab + placebo + carboplatin/etoposide	PFS (not- reached); OS (not- reached)
TRIPLEX (NCT05223647)	III	I line	Extended	302	durvalumab + platinum/etoposide + thoracic RT vs durvalumab + platinum/etoposide	OS
CASPIAN-RT (NCT05161533)	II	I line	Extended	50	durvalumab + platinum/etoposide + thoracic RT	PFS

RAPTOR (NCT04402788)	II/III	maintenance after I line	Extended	138	atezolizumab + thoracic RT vs atezolizumab	PFS; OS
EA5161 (NCT03382561)	II	I line	Extended	150	nivolumab + platinum/etoposide	PFS
PAVE (NCT03568097)	II	I line	Extended	55	avelumab + platinum/etoposide	PFS
PRIO (NCT04728230)	I/II	I line	Extended	63	durvalumab + platinum/etoposide + olaparib +/- thoracic RT	safety
NCT05552846	II	I line	Extended	104	Anti-PD1/PD-L1 + platinum/etoposide + thoracic RT	PFS
NCT05484583	II	I line	Extended	58	durvalumab + platinum/etoposide + thoracic RT	OS
NCT05403723	Ib	I line	Extended	50	durvalumab + platinum/etoposide + SBRT	safety
JAVELIN Medley (NCT02554812)	Ib/II	≥ II line	Extended	NA	avelumab + utomilumab (anti-4-1BB antibody)	safety; ORR
NCT04919382	II	II line	Extended	56	atezolizumab + temozolomide	ORR
NCT03728361	II	II line	Extended	55	nivolumab + temozolomide	ORR

Table 1. Ongoing studies currently investigating immune-checkpoint inhibitors alone or in combination with chemotherapy or other agents, including radiotherapy, both in extended and limited disease-small cell lung cancer. Abbreviations: pts: patients; cCRT: concurrent chemo-radiotherapy; RT: radiotherapy; SBRT: stereotactic body radiation therapy; OS: overall survival; PFS: progression free survival; DFS: disease free survival; ORR: objective response rate.

4. Other therapeutic strategies in SCLC:

Beside immunotherapy, recent advances in understanding the molecular biology of SCLC and its integration with the new classification of SCLC into the four molecular subtypes have provided the identification of novel potential therapeutic opportunities [8,94] (**Figure 2**).

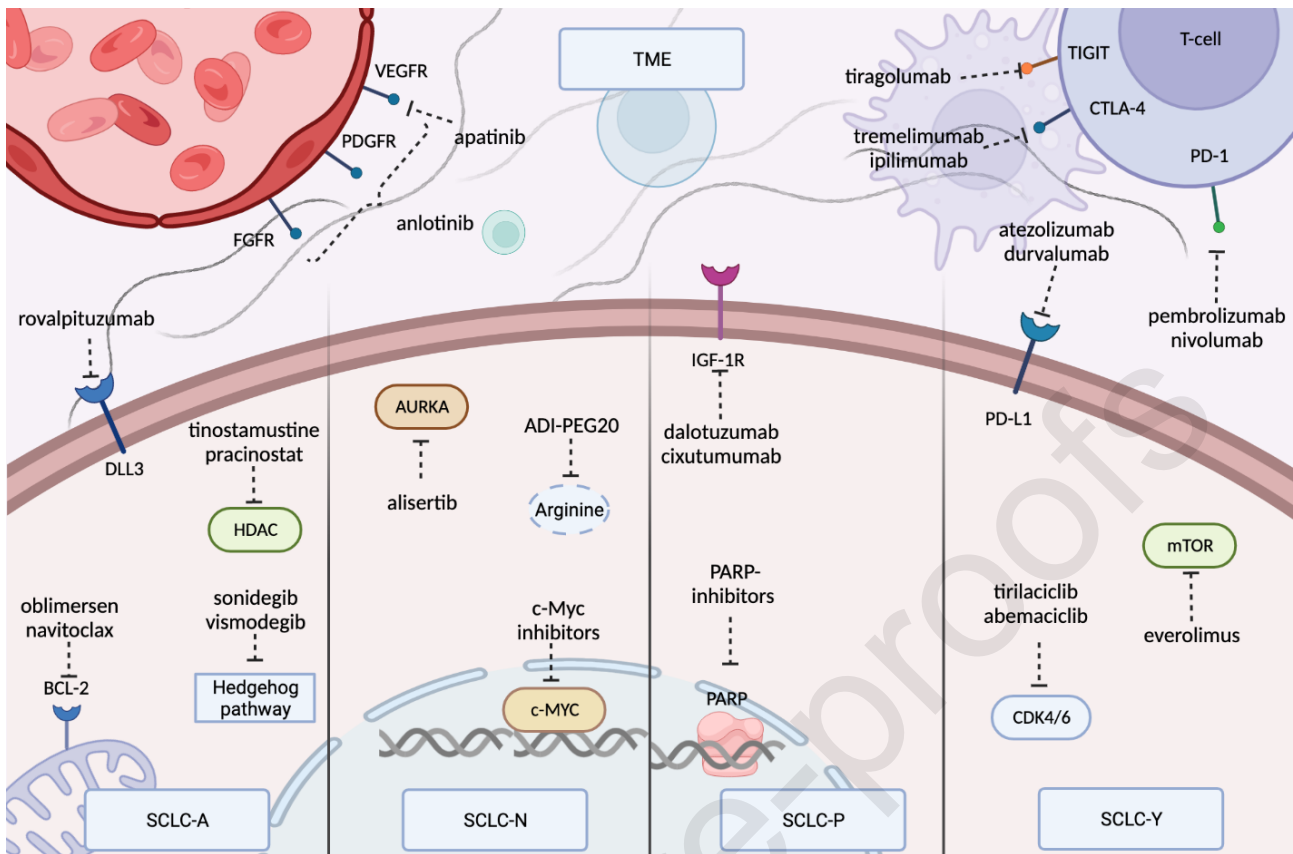


Figure 2. Potential therapeutic options in SCLC subtypes according to molecular classification. The different expression of key transcription regulators define four different subtypes of SCLC (i.e. SCLC-A, SCLC-N, SCLC-P, SCLC-Y), each of which exhibits a peculiar sensitivity to different therapeutic approaches.

4.1 Therapeutic strategies for SCLC-A subtype

Delta-like ligand 3 protein (DLL3) is a surface marker expressed in most SCLC patients [95] that acts as an inhibitor of the tumor-suppressor gene NOTCH1 [96] and is linked to the expression of the transcription factor ASCL1 [97]. Therefore, DLL3 may represent an interesting therapeutic target in SCLC-A molecular subtype. Rovalpituzumab tesirine (Rova-T) is a first-in-class antibody drug conjugate targeting DLL3 that showed promising activity in preclinical and early phase clinical studies [98,99]. However, the phase 2 TRINITY study, which assessed safety and efficacy of Rova-T in DLL3-expressing SCLC in the third-line and beyond setting, was less promising, showing an ORR of 14.3% and an OS of 5.7 months in patients with DLL3-high SCLC [100]. Moreover, the enrollment of two phase 3 studies (TAHOE and MERU trials), evaluating second-line treatment and first-line maintenance therapy of Rova-T in advanced SCLC, was discontinued for futility after pre-planned interim analysis and development of Rova-T was halted [101,102].

The Bcl-2 oncogene protein is a druggable protein, highly expressed in approximately 65% of SCLC patients [103]. Bcl-2 is transcriptional target of ASCL1 and an increased susceptibility to Bcl-2 inhibition was described in SCLC-A subtype [9]. However, the Bcl-2 antisense oligonucleotide oblimersen did not improve any clinical outcome measure in therapy-naïve patients with ED-SCLC [104]. Similarly, no relevant clinical benefit was achieved with the potent Bcl-2 inhibitor navitoclax (ABT-263) while a significant thrombocytopenia was reported [105]. Safety of a novel dual Bcl-2/Bcl-xL inhibitor, palcitoclax (APG-125), was also investigated in two phase 1 study in patients with refractory SCLC (NCT03387332 and NCT03080311) [106].

SCLC-A subtype is also associated with the inactivation of the cAMP response element binding protein (CREBBP), an acetyltransferase that mediates the chromatin accessibility. Pre-clinical data showed that CREBBP acts as a potent tumor suppressor and its loss reduces histone acetylation and transcription of cellular adhesion genes, while driving tumorigenesis. Inactivation of CREBBP by histone deacetylase inhibitors (HDAC-i), such as pracinostat, enhances responses in CREBBP-mutant SCLC [107]. Tinostamustine (EDO-S101) is a first-in-class HDAC-i that is currently being

evaluated in a phase 1/2 study enrolling patients with solid tumors, including relapsed SCLC (NCT03345485) [108].

Lastly, the SOX2 oncogene, which encodes for a transcriptional regulator of pluripotent stem cells, is frequently upregulated in the SCLC-A subtype and is regulated by the hedgehog signal cascade in addition to mTOR and JAK/STAT pathways [109,110]. A phase I trial of the hedgehog inhibitor, sonidegib, in combination with etoposide and cisplatin, showed an ORR of 79% and a DCR of 100% in 14 untreated patients with ED-SCLC [111]. However, a phase 2 study of platinum-based CT in combination with the hedgehog inhibitor vismodegib for the initial treatment of patients with ED-SCLC showed no improvement in PFS and OS [112].

4.2 Therapeutic strategies for SCLC-N subtype

A further potential target for patients with SCLC is Aurora kinase A (AURKA), a key regulator of mitosis which is amplified or overexpressed in several solid tumors, including SCLC, and may play a role in tumorigenesis. The AURKA inhibitor, Alisertib, showed efficacy as monotherapy in a phase 2 trial, achieving an ORR of 48% [113]. Alisertib was also studied in association with paclitaxel as a second-line treatment for SCLC reporting a mPFS of 3.32 months with alisertib/paclitaxel versus 2.17 months with placebo/paclitaxel (HR: 0.77; 95% CI, 0.557–1.067). Furthermore, a subset of patients with c-Myc expression showed significantly improved PFS with alisertib/paclitaxel, confirming that the MYC gene amplification, frequently found in SCLC-N subtype, could be associated with improved sensitivity to AURKA inhibitors [114]. Accordingly, a combination strategy of AURKA and c-MYC inhibitors may improve therapeutic efficacy in this specific subtype [115]. Moreover, recent data suggest arginine deprivation caused by pegylated arginine deiminase (ADI-PEG 20) as a specific therapeutic vulnerability for MYC-driven tumors, including SCLC-N subtype [116].

4.3 Therapeutic strategies for SCLC-P subtype

POU2F3-expressing SCLC lines showed a dependence on the receptor tyrosine kinase IGF-1R (insulin-like growth factor 1 receptor) that is frequently overexpressed in SCLC-P subtype and is associated with a dismal prognosis. Consequently, IGF-1R may serve as a potential therapeutic target for these patients [117–119]. Dalotuzumab, a IGF-1R inhibitor, was tested in a phase I study in combination with CT, showing an ORR of 67% [120], while the IGF-1R tyrosine kinase inhibitor linsitinib showed no clinical activity in unselected relapsed SCLC patients vs topotecan [121,122]. Another phase 2 study, that evaluated platinum-based CT in combination with hedgehog-inhibitor vismodegib or with the IGF-1R antagonist cixutumumab in ED-SCLC patients, did not report an improved PFS or OS for neither vismodegib nor cixutumumab [112].

SCLC is characterized by aberrant expression of several genes encoding for proteins involved in DNA damage repair, such as PARP enzymes. Accordingly, it has been reported that PARP-i have single-agent activity in SCLC models and enhance the effect of cytotoxic agents, in particular in the SCLC-P subtype [123]. When administered as single agents, the PARP-i olaparib and talazoparib showed modest clinical activity [124–126], while the PARP-i veliparib has shown to be active in combination with temozolomide in preclinical study [127]. In a phase 2 randomized trial, the addition of the PARP-i veliparib to temozolomide (TMZ) demonstrated a significant improvement in ORR (39 vs 19%, $p=0.016$) in refractory SCLC, but did not prolong PFS and OS. However, an exploratory analysis of Schlafen-11 (SLFN11) expression (a DNA/RNA helicase which regulates response to DNA damage and replication stress) demonstrated a significantly prolonged PFS (5.7 vs 3.6 months, $p=0.009$) and OS (12.2 vs 7.5 months $p=0.014$) in patients with SLFN11-positive tumors treated with TMZ/veliparib, suggesting a promising biomarker of PARP-i sensitivity in SCLC [128,129]. More recently, other phase 2 studies demonstrated a benefit of PARP-i olaparib and talazoparib in combination with low-dose TMZ in refractory SCLC [130,131]. In addition, in patients with treatment-naïve ED-SCLC the addition of veliparib to frontline CT showed a sign of efficacy and improved PFS and OS in a randomized phase 2 trial [132]. Similarly, a phase 2 study of veliparib plus platinum-CT followed by veliparib maintenance demonstrated an improved mPFS versus control (HR: 0.67, CI 80% 0.50-0.88; $p=0.059$) and a trend toward longer PFS with veliparib in SLFN11-positive patients (HR: 0.6, CI 80%, 0.36-0.97), without a corresponding benefit in OS

[133]. Another PARP-i, niraparib, as maintenance therapy has recently shown only modest improvement in PFS for patients with platinum-responsive ED-SCLC [134]. PARP-inhibitors are currently being evaluated in combination with ICIs in several studies (NCT04334941, NCT03830918, NCT04701307, NCT04728230) and preliminary data have demonstrated the effectiveness and safety of this combination. Olaparib with pembrolizumab as second-line treatment showed in particular an ORR of 45.5% and a DCR of 81.8% in 21 patients with ED-SCLC [135], while a phase 2 trial of olaparib plus durvalumab suggested that tumor immune phenotypes may be relevant for SCLC responses to ICIs combinations [136].

4.4 Therapeutic strategies for SCLC-Y subtype

The molecular SCLC-Y subtype is preferentially linked to the immune blockade targeting the PD-1/PD-L1 axis, since YAP1 expression has been shown to upregulate PD-L1 transcripts and induce an immunosuppressive tumor microenvironment. Also, the higher expression of CD38 and LAG-3 in SCLC-Y tumor cells makes this SCLC subtype more responsive to ICIs [8,137,138]. Beside immunotherapy, based on recent preclinical data, SCLC cell lines with high YAP1 expression also showed relatively higher sensitivity to mTOR (mammalian target of rapamycin) and PLK (polo-like kinase) inhibitors [139]. The mTOR inhibitor everolimus was tested as monotherapy in 35 relapsed SCLC patients, but yielded a low rate of disease control (26%) [140]. As a combined strategy, everolimus was also investigated in two phase Ib studies in association with CT: in 21 previously treated SCLC patients everolimus with paclitaxel showed an ORR of 28% [141], while as first line therapy in combination with cisplatin and etoposide an ORR of 58.2% and a mPFS of 35.1 weeks were reported [142]. However, given the limited results obtained, no further evaluations were performed for everolimus in phase 3 studies. Finally, based on recent *in vitro* results, YAP1 was shown to be downstream of the retinoblastoma protein (RB1) and associated with decreased drug sensitivity. As RB1 expression in SCLC cell lines sensitizes them to CDK4/6 inhibitors, this class of drugs may be tested for efficacy in SCLC-Y subtype [139,143].

4.5 Therapeutic strategies irrespective to molecular subtypes: targeting the vascular system and lurbinctedin

SCLC proliferation has been shown to be closely dependent on micro-vessels formation. Accordingly, vascular endothelial growth factor (VEGF) is over-expressed in SCLC and is associated with poor prognosis [144,145]. Inhibition of angiogenesis could be a promising strategy for SCLC treatment and the efficacy of the anti-VEGF antibody bevacizumab and the small molecules tyrosine kinase inhibitors (TKIs) directed against the VEGF receptor (VEGF-R) has been investigated in several studies [146]. The phase 2 SALUTE trial randomly assigned ED-SCLC patients to receive bevacizumab or placebo added to platinum-CT. mPFS was improved in the bevacizumab over the placebo arm, while OS was similar for both groups [147]. In the IFCT-0802 phase 2 trial, in which patients who responded to induction CT were randomized to receive four additional cycles of CT alone or in combination with bevacizumab, no significant differences between the two groups in PFS or OS were reported [148]. Finally, a randomized controlled phase 3 trial was conducted to definitively assess the efficacy of bevacizumab in combination with first-line CT for ED-SCLC. The addition of bevacizumab led to a small, but statistically significant improvement in PFS (mPFS 6.7 vs 5.7 months in the experimental and control arm, respectively; HR: 0.72, 95% CI 0.54–0.97; $p=0.030$), but not in OS (mOS 9.8 vs 8.9 months; HR 0.78, 95% CI 0.58–1.06) [149]. Oral multi-TKIs (vandetanib, sunitinib and sorafenib) have been evaluated in several studies and in different clinical settings for patients with SCLC. However, reported efficacy and activity were limited, with no or only modest improvements in clinical outcomes [150–155]. Anlotinib is a new VEGFR inhibitor recently approved by China Food and Drug Administration as third-line treatment for ED-SCLC, thanks to results obtained in a randomized phase 2 study (ALTER 1202) where it showed prolonged PFS and OS in the experimental group (mPFS: 4.3 vs 0.7 months; HR: 0.19, $p<0.0001$ and mOS: 7.3 vs 4.9 months; HR: 0.53, $p<0.0029$) [156]. Another VEGFR-2 inhibitor, apatinib, was evaluated for pretreated SCLC patients in different trials, reporting an ORR from 13.6% to 17.5% and modest improvement in PFS and OS [157,158]. Finally, the PASSION phase 2 trial investigated the activity and safety of apatinib plus

camrelizumab (a PD-1 inhibitor), in patients with recurrent ED-SCLC. An ORR was observed in 34% patients, while mPFS and OS were 3.6 and 8.4 months, respectively [159].

Lurbinectedin is a novel anticancer drug that inhibits oncogenic transcription activity in tumor cells. It impairs in particular the formation of RNA by limiting the binding of transcription factors to their promoters, inducing the accumulation of DNA double-strand breaks and eventually leading to cell death [160,161]. Additionally, lurbinectedin reduces the inflammatory TME and decreases transcription within tumor-associated macrophages, which may lead to reduced tumor cell survival, reduced angiogenesis and improved anti-tumor immunity [162]. Consistent with its mechanism of action, lurbinectedin has an enhanced activity in cancers with defects in DNA mismatch repair, including SCLC. In a basket trial of 105 patients with relapsed SCLC, lurbinectedin showed a manageable safety profile and promising activity. In detail, the reported ORR was 35.2%, while the mPFS and mOS were 3.5 and 9.3 months, respectively [163]. According to these data, in 2020 lurbinectedin has been granted orphan drug status by the EMA as well as accelerated FDA approval for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based CT. Consistent with the synergistic effects found in preclinical studies, lurbinectedin plus doxorubicin showed high activity in patients with recurrent SCLC [164]. This combination was then studied in the randomized phase 3 ATLANTIS trial, which included 613 patients who had failed a previous platinum-containing regimen. Although the primary objective of this study OS was not met, the combination of lurbinectedin plus doxorubicin resulted active, especially in relapsed SCLC patients with sensitive disease (CT free interval ≥ 90 days) and without CNS involvement [165]. Recently, a post-hoc analysis of 50 patients who completed 10 cycles of lurbinectedin/doxorubicin combination and switched to lurbinectedin monotherapy, showed a maintenance or improvement of tumor response, with favorable OS and DOR [166]. Lurbinectedin is currently being studied in other combinations, including irinotecan (NCT05153239) and ICIs (NCT04358237, NCT04610658, NCT05091567, NCT04607954). A preliminary analysis from the phase 1/2 LUPER (NCT04358237) study that evaluated lurbinectedin with pembrolizumab was recently reported, demonstrating a manageable safety profile and preliminary efficacy data (ORR 30.8% and DOR 2.1 months) [167].

5. Conclusions

In the last decades, few significant clinical improvements in the outcomes of SCLC have been achieved. However, the introduction of ICIs in clinical practice has given hope in the treatment of patients with SCLC. Also, recent progress in defining a novel molecular classification and the identification of biological pathways driving SCLC have provided multiple novel potential therapeutic strategies. Preclinical data provide scientific bases for combining immunotherapy with standard platinum-based CT and results from recent randomized trials confirm the effectiveness of this therapeutic approach. Many other therapeutic strategies have been evaluated in preclinical models and early phase studies and some promising results have been obtained with new agents, such as inhibitors of angiogenesis (i.e. bevacizumab, apatinib, anlotinib) and of oncogenic transcription (lurbinectedin).

SCLC is now being stratified into functional and molecular categories, although patients are still enrolled in clinical trials irrespective of their molecular background. The new classification into subtypes based on expression of transcription factors and immune infiltrate (SCLC-A, SCLC-N, SCLC-P, SCLC-Y and SCLC-I) may be a prerequisite for the development of biomarker-targeted therapy and, likely, would be crucial for choosing the most effective therapy for SCLC patients. Moreover, the effective development of an optimal targeted treatment should require the identification of clinically meaningful biomarkers. Since ICIs, CT and biomarker-directed therapies, operate on different targets and mechanisms, rational drug combinations or synergistic treatment may increase the therapeutic effects in SCLC.

However, although the pace of laboratory research on SCLC has accelerated considerably and several novel drugs are being actively pursued, many gaps still remain in the characterization of SCLC. A deeper understanding of molecular alterations in SCLC could provide the identification of

new combination strategies and, ultimately, the development of new molecularly guided treatments and subtype-specific therapies, which are essential to tackle this lethal malignancy.

Funding: The authors declared no specific grant for this review from any funding agencies in the public, commercial, or not-for-profit sectors

CRediT authorship contribution statement

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Declarations of Competing Interest: The authors state that they have no relevant affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the topics or materials discussed in the present manuscript.

Acknowledgement: The authors are grateful to Irida Gjyshi for her help in revising the English in the final version of the manuscript

References

1. Meerbeeck, J.P. Van; Fennell, D.A.; Ruyscher, D.K.M. De Small-cell lung cancer. *Lancet* **2011**, *378*, 1741–1755, doi:10.1016/S0140-6736(11)60165-7.
2. Govindan, R.; Page, N.; Morgensztern, D.; Read, W.; Tierney, R.; Vlahiotis, A.; Spitznagel, E.L.; Piccirillo, J. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. *J. Clin. Oncol.* **2006**, *24*, 4539–4544, doi:10.1200/JCO.2005.04.4859.
3. Peifer, M.; Fernández-Cuesta, L.; Sos, M.L.; George, J.; Seidel, D.; Kasper, L.H.; Plenker, D.; Leenders, F.; Sun, R.; Zander, T.; et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat. Genet.* **2012**, *44*, 1104–1110, doi:10.1038/ng.2396.

4. Rudin, C.M.; Durinck, S.; Stawiski, E.W.; Poirier, J.T.; Modrusan, Z.; Shames, D.S.; Bergbower, E.A.; Guan, Y.; Shin, J.; Guillory, J.; et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat. Genet.* **2012**, *44*, 1111–1116, doi:10.1038/NG.2405.
5. George, J.; Lim, J.S.; Jang, S.J.; Cun, Y.; Ozretia, L.; Kong, G.; Leenders, F.; Lu, X.; Fernández-Cuesta, L.; Bosco, G.; et al. Comprehensive genomic profiles of small cell lung cancer. *Nature* **2015**, *524*, 47–53, doi:10.1038/nature14664.
6. Arcaro, A. Targeted therapies for small cell lung cancer: Where do we stand? *Crit. Rev. Oncol. Hematol.* **2015**, *95*, 154–164, doi:10.1016/j.critrevonc.2015.03.001.
7. Gazdar, A.F.; Bunn, P.A.; Minna, J.D. Small-cell lung cancer : what we know , what we need to know and the path forward. *Nat. Rev. Cancer* **2017**, *17*, 725–735, doi:10.1038/nrc.2017.87.
8. Rudin, C.M.; Poirier, J.T.; Byers, L.A.; Dive, C.; Dowlati, A.; George, J.; Heymach, J. V.; Johnson, J.E.; Lehman, J.M.; MacPherson, D.; et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat. Rev. Cancer* **2019**, *19*, 289–297, doi:10.1038/s41568-019-0133-9.
9. Gay, C.M.; Stewart, C.A.; Park, E.M.; Diao, L.; Groves, S.M.; Heeke, S.; Nabet, B.Y.; Fujimoto, J.; Solis, L.M.; Lu, W.; et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell* **2021**, *39*, 346–360, doi:10.1016/j.ccell.2020.12.014.
10. Frese, K.K.; Simpson, K.L.; Dive, C. Small cell lung cancer enters the era of precision medicine. *Cancer Cell* **2021**, *39*, 297–299, doi:10.1016/j.ccell.2021.02.002.
11. Baine, M.K.; Hsieh, M.S.; Lai, W.V.; Egger, J. V.; Jungbluth, A.A.; Daneshbod, Y.; Beras, A.; Spencer, R.; Lopardo, J.; Bodd, F.; et al. SCLC Subtypes Defined by ASCL1, NEUROD1, POU2F3, and YAP1: A Comprehensive Immunohistochemical and Histopathologic Characterization. *J. Thorac. Oncol.* **2020**, *15*, 1823–1835, doi:10.1016/j.jtho.2020.09.009.
12. Pearsall, S.M.; Humphrey, S.; Reville, M.; Morgan, D.; Frese, K.K.; Galvin, M.; Kerr, A.; Carter, M.; Priest, L.; Blackhall, F.; et al. The Rare YAP1 Subtype of SCLC Revisited in a Biobank of 39 Circulating Tumor Cell Patient Derived Explant Models: A Brief Report. *J. Thorac. Oncol.* **2020**, *15*, 1836–1843, doi:10.1016/j.jtho.2020.07.008.
13. Horn, L.; Mansfield, A.S.; Szczyńska, A.; Havel, L.; Krzakowski, M.; Hochmair, M.J.; Huemer, F.; Losonczy, G.; Johnson, M.L.; Nishio, M.; et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *379*, 2220–2229, doi:10.1056/nejmoa1809064.
14. Paz-Ares, L.; Dvorkin, M.; Chen, Y.; Reinmuth, N.; Hotta, K.; Trukhin, D.; Statsenko, G.; Hochmair, M.J.; Özgüroğlu, M.; Ji, J.H.; et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* **2019**, *394*, 1929–1939, doi:10.1016/S0140-6736(19)32222-6.
15. Bunn, P.A.; Minna, J.D.; Augustyn, A.; Gazdar, A.F.; Ouadah, Y.; Krasnow, M.A.; Berns, A.; Brambilla, E.; Rekhtman, N.; Massion, P.P.; et al. Small cell lung cancer: Can recent advances in biology and molecular biology be translated into improved outcomes? *J. Thorac. Oncol.* **2016**, *11*, 453–474, doi:10.1016/j.jtho.2016.01.012.
16. Gadgeel, S.M. Targeted Therapy and Immune Therapy for Small Cell Lung Cancer. *Curr. Treat. Options Oncol.* **2018**, *19*, doi:10.1007/s11864-018-0568-3.
17. Mak, D.W.S.; Li, S.; Minchom, A. Challenging the recalcitrant disease—developing molecularly driven treatments for small cell lung cancer. *Eur. J. Cancer* **2019**, *119*, 132–150, doi:10.1016/j.ejca.2019.04.037.

18. Reck, M.; Heigener, D.; Reinmuth, N. Immunotherapy for Lung Cancer. *Futur. Oncol.* **2016**, *12*, 931–943, doi:10.1159/000446726.
19. Calles, A.; Aguado, G.; Sandoval, C.; Álvarez, R. The role of immunotherapy in small cell lung cancer. *Clin. Transl. Oncol.* **2019**, *21*, 961–976, doi:10.1007/s12094-018-02011-9.
20. Remon, J.; Aldea, M.; Besse, B.; Planchard, D.; Reck, M.; Giaccone, G.; Soria, J.C. Small cell lung cancer: a slightly less orphan disease after immunotherapy. *Ann. Oncol.* **2021**, *32*, 698–709, doi:10.1016/j.annonc.2021.02.025.
21. Darnell, R.B. the Intersection of Cancer , Immunity , and the Brain. *Proc. Natl. Acad. Sci. U. S. A.* **1996**, *93*, 4529–4536.
22. Gozzard, P.; Chapman, C.; Vincent, A.; Lang, B.; Maddison, P. Novel humoral prognostic markers in small-cell lung carcinoma: A prospective study. *PLoS One* **2015**, *10*, 1–14, doi:10.1371/journal.pone.0143558.
23. Maddison, P.; Newsome-Davis, J.; Mills, K.R.; Souhami, robert L. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet* **1999**, *353*, 117–118.
24. Darnell, R.B.; DeAngelis, L.M. Regression of small-cell lung carcinoma in patients with paraneoplastic neuronal antibodies. *Lancet* **1993**, *341*, 21–22, doi:10.1016/0140-6736(93)92485-C.
25. Iams, W.T.; Shiuan, E.; Meador, C.B.; Roth, M.; Bordeaux, J.; Vaupel, C.; Boyd, K.L.; Summitt, I.S.B.; Wang, L.L.; Schneider, J.T.; et al. Improved Prognosis and Increased Tumor-Infiltrating Lymphocytes in Patients Who Have SCLC With Neurologic Paraneoplastic Syndromes. *J. Thorac. Oncol.* **2019**, *14*, 1970–1981, doi:10.1016/j.jtho.2019.05.042.
26. Alexandrov, L.B.; Ju, Y.S.; Haase, K.; Van Loo, P.; Martincorena, I.; Nik-Zainal, S.; Totoki, Y.; Fujimoto, A.; Nakagawa, H.; Shibata, T.; et al. Mutational signatures associated with tobacco smoking in human cancer. *Science (80-)*. **2016**, *354*, 618–622, doi:10.1126/science.aag0299.
27. Pleasance, E.D.; Stephens, P.J.; O'Meara, S.; McBride, D.J.; Meynert, A.; Jones, D.; Lin, M.L.; Beare, D.; Lau, K.W.; Greenman, C.; et al. A small-cell lung cancer genome with complex signatures of tobacco exposure. *Nature* **2010**, *463*, 184–190, doi:10.1038/nature08629.
28. McGranahan, N.; Furness, A.J.S.; Rosenthal, R.; Ramskov, S.; Lyngaa, R.; Saini, S.K.; Jamal-Hanjani, M.; Wilson, G.A.; Birkbak, N.J.; Hiley, C.T.; et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science (80-)*. **2016**, *351*, 1463–1469, doi:10.1126/science.aaf1490.
29. Matsushita, H.; Vesely, M.D.; Koboldt, D.C.; Rickert, C.G.; Uppaluri, R.; Magrini, V.J.; Arthur, C.D.; White, J.M.; Chen, Y.S.; Shea, L.K.; et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. *Nature* **2012**, *482*, 400–404, doi:10.1038/nature10755.
30. Goodman, A.M.; Kato, S.; Bazhenova, L.; Patel, S.P.; Frampton, G.M.; Miller, V.; Stephens, P.J.; Daniels, G.A.; Kurzrock, R. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol. Cancer Ther.* **2017**, *16*, 2598–2608, doi:10.1158/1535-7163.MCT-17-0386.
31. Hellmann, M.D.; Callahan, M.K.; Awad, M.M.; Calvo, E.; Ascierto, P.A.; Atmaca, A.; Rizvi, N.A.; Hirsch, F.R.; Selvaggi, G.; Szustakowski, J.D.; et al. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. *Cancer Cell* **2018**, *33*, 853-861.e4, doi:10.1016/j.ccell.2018.04.001.
32. Hellmann, M.D.; Ciuleanu, T.-E.; Pluzanski, A.; Lee, J.S.; Otterson, G.A.; Audigier-Valette,

- C.; Minenza, E.; Linardou, H.; Burgers, S.; Salman, P.; et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N. Engl. J. Med.* **2018**, *378*, 2093–2104, doi:10.1056/nejmoa1801946.
33. Spigel, D.R.; Socinski, M.A. Rationale for chemotherapy, immunotherapy, and checkpoint blockade in SCLC: Beyond traditional treatment approaches. *J. Thorac. Oncol.* **2013**, *8*, 587–598, doi:10.1097/JTO.0b013e318286cf88.
34. Tian, Y.; Zhai, X.; Han, A.; Zhu, H.; Yu, J. Potential immune escape mechanisms underlying the distinct clinical outcome of immune checkpoint blockades in small cell lung cancer. *J. Hematol. Oncol.* **2019**, *12*, 1–12, doi:10.1186/s13045-019-0753-2.
35. Muppa, P.; Parrilha Terra, S.B.S.; Sharma, A.; Mansfield, A.S.; Aubry, M.C.; Bhinge, K.; Asiedu, M.K.; de Andrade, M.; Janaki, N.; Murphy, S.J.; et al. Immune Cell Infiltration May Be a Key Determinant of Long-Term Survival in Small Cell Lung Cancer. *J. Thorac. Oncol.* **2019**, *14*, 1286–1295, doi:10.1016/j.jtho.2019.03.028.
36. Carvajal-Hausdorf, D.; Altan, M.; Velcheti, V.; Gettinger, S.N.; Herbst, R.S.; Rimm, D.L.; Schalper, K.A. Expression and clinical significance of PD-L1, B7-H3, B7-H4 and TILs in human small cell lung Cancer (SCLC). *J. Immunother. Cancer* **2019**, *7*, 1–9, doi:10.1186/s40425-019-0540-1.
37. Tian, T.; Gu, X.; Zhang, B.; Liu, Y.; Yuan, C.; Shao, L.; Guo, Y.; Fan, K. Increased circulating CD14(+)HLA-DR-/low myeloid-derived suppressor cells are associated with poor prognosis in patients with small-cell lung cancer. *Cancer Biomarkers* **2015**, *15*, 425–432, doi:10.3233/CBM-150473.
38. Wang, W.; Hodgkinson, P.; McLaren, F.; MacKinnon, A.; Wallace, W.; Howie, S.; Sethi, T. Small cell lung cancer tumour cells induce regulatory T lymphocytes, and patient survival correlates negatively with FOXP3+ cells in tumour infiltrate. *Int. J. Cancer* **2012**, *131*, 928–937, doi:10.1002/ijc.27613.
39. Dora, D.; Rivard, C.; Yu, H.; Bunn, P.; Suda, K.; Ren, S.; Lueke Pickard, S.; Laszlo, V.; Harko, T.; Megyesfalvi, Z.; et al. Neuroendocrine subtypes of small cell lung cancer differ in terms of immune microenvironment and checkpoint molecule distribution. *Mol. Oncol.* **2020**, *14*, 1947–1965, doi:10.1002/1878-0261.12741.
40. Gazdar, A. MS32.04 Molecular Phenotypes of SCLC. *J. Thorac. Oncol.* **2018**, *13*, S309, doi:10.1016/j.jtho.2018.08.211.
41. Chan, J.M.; Quintanal-Villalonga, Á.; Gao, V.R.; Xie, Y.; Allaj, V.; Chaudhary, O.; Masilionis, I.; Egger, J.; Chow, A.; Walle, T.; et al. Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. *Cancer Cell* **2021**, *39*, 1479-1496.e18, doi:10.1016/j.ccell.2021.09.008.
42. Best, S.A.; Hess, J.B.; Souza-Fonseca-Guimaraes, F.; Cursons, J.; Kersbergen, A.; Dong, X.; Rautela, J.; Hyslop, S.R.; Ritchie, M.E.; Davis, M.J.; et al. Harnessing Natural Killer Immunity in Metastatic SCLC. *J. Thorac. Oncol.* **2020**, *15*, 1507–1521, doi:10.1016/j.jtho.2020.05.008.
43. Zhu, M.; Huang, Y.; Bender, M.E.; Girard, L.; Kollipara, R.; Eglenen-Polat, B.; Naito, Y.; Savage, T.K.; Huffman, K.E.; Koyama, S.; et al. Evasion of innate immunity contributes to small cell lung cancer progression and metastasis. *Cancer Res.* **2021**, *81*, 1813–1826, doi:10.1158/0008-5472.CAN-20-2808.
44. Inamura, K.; Yokouchi, Y.; Kobayashi, M.; Ninomiya, H.; Sakakibara, R.; Nishio, M.; Okumura, S.; Ishikawa, Y. Relationship of tumor PD-L1 (CD274) expression with lower mortality in lung high-grade neuroendocrine tumor. *Cancer Med.* **2017**, *6*, 2347–2356, doi:10.1002/cam4.1172.
45. Berghoff, A.S.; Ricken, G.; Wilhelm, D.; Rajky, O.; Widhalm, G.; Dieckmann, K.; Birner, P.;

- Bartsch, R.; Preusser, M. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). *J. Neurooncol.* **2016**, *130*, 19–29, doi:10.1007/s11060-016-2216-8.
46. Gadgeel, S.M.; Pennell, N.A.; Fidler, M.J.; Halmos, B.; Bonomi, P.; Stevenson, J.; Schneider, B.; Sukari, A.; Ventimiglia, J.; Chen, W.; et al. Phase II Study of Maintenance Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC). *J. Thorac. Oncol.* **2018**, *13*, 1393–1399, doi:10.1016/j.jtho.2018.05.002.
47. Chung, H.C.; Lopez-Martin, J.A.; Kao, S.C.-H.; Miller, W.H.; Ros, W.; Gao, B.; Marabelle, A.; Gottfried, M.; Zer, A.; Delord, J.-P.; et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *J. Clin. Oncol.* **2018**, *36*, 8506, doi:10.1200/JCO.2018.36.15_suppl.8506.
48. Ott, P.A.; Elez, E.; Hirt, S.; Kim, D.W.; Morosky, A.; Saraf, S.; Piperdi, B.; Mehnert, J.M. Pembrolizumab in patients with extensive-stage small-cell lung cancer: Results from the phase Ib KEYNOTE-028 study. *J. Clin. Oncol.* **2017**, *35*, 3823–3829, doi:10.1200/jco.2017.72.5069.
49. Antonia, S.J.; López-Martin, J.A.; Bendell, J.; Ott, P.A.; Taylor, M.; Eder, J.P.; Jäger, D.; Pietanza, M.C.; Le, D.T.; de Braud, F.; et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* **2016**, *17*, 883–895, doi:10.1016/S1470-2045(16)30098-5.
50. Yu, H.; Batenchuk, C.; Badzio, A.; Boyle, T.A.; Czapiewski, P.; Chan, D.C.; Lu, X.; Gao, D.; Ellison, K.; Kowalewski, A.A.; et al. PD-L1 Expression by Two Complementary Diagnostic Assays and mRNA In Situ Hybridization in Small Cell Lung Cancer. *J. Thorac. Oncol.* **2017**, *12*, 110–120, doi:10.1016/j.jtho.2016.09.002.
51. Kim, H.S.; Lee, J.H.; Nam, S.J.; Ock, C.Y.; Moon, J.W.; Yoo, C.W.; Lee, G.K.; Han, J.Y. Association of PD-L1 Expression with Tumor-Infiltrating Immune Cells and Mutation Burden in High-Grade Neuroendocrine Carcinoma of the Lung. *J. Thorac. Oncol.* **2018**, *13*, 636–648, doi:10.1016/j.jtho.2018.01.008.
52. Komiya, T.; Madan, R. PD-L1 expression in small cell lung cancer. *Eur. J. Cancer* **2015**, *51*, 1853–1855, doi:10.1016/j.ejca.2015.06.003.
53. Yasuda, Y.; Ozasa, H.; Kim, Y.H. PD-L1 Expression in Small Cell Lung Cancer. *J. Thorac. Oncol.* **2018**, *13*, e40–e41, doi:10.1016/j.jtho.2017.10.013.
54. Bonanno, L.; Pavan, A.; Dieci, M. V.; Di Liso, E.; Schiavon, M.; Comacchio, G.; Attili, I.; Pasello, G.; Calabrese, F.; Rea, F.; et al. The role of immune microenvironment in small-cell lung cancer: Distribution of PD-L1 expression and prognostic role of FOXP3-positive tumour infiltrating lymphocytes. *Eur. J. Cancer* **2018**, *101*, 191–200, doi:10.1016/j.ejca.2018.06.023.
55. Santarpià, M.; Karachaliou, N. Tumor immune microenvironment characterization and response to anti-PD-1 therapy. *Cancer Biol. Med.* **2015**, *12*, 74–78, doi:10.7497/j.issn.2095-3941.2015.0022.
56. Liu, S. V.; Reck, M.; Mansfield, A.S.; Mok, T.; Scherpereel, A.; Reinmuth, N.; Garassino, M.C.; De Castro Carpeno, J.; Califano, R.; Nishio, M.; et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). *J. Clin. Oncol.* **2021**, *39*, 619–630.
57. Suh, W.-K.; Gajewska, B.U.; Okada, H.; Gronski, M.A.; Bertram, E.M.; Dawicki, W.; Duncan, G.S.; Bukczynski, J.; Plyte, S.; Elia, A.; et al. The B7 family member B7-H3 preferentially down-regulates T helper type 1-mediated immune responses. *Nat. Immunol.* **2003**, *4*, 899–906, doi:10.1038/ni967.
58. Zhang, W.; Huang, Q.; Xiao, W.; Zhao, Y.; Pi, J.; Xu, H.; Zhao, H.; Xu, J.; Evans, C.E.; Jin,

- H. Advances in Anti-Tumor Treatments Targeting the CD47/SIRP α Axis. *Front. Immunol.* **2020**, *11*, 18, doi:10.3389/fimmu.2020.00018.
59. Weiskopf, K.; Jahchan, N.S.; Schnorr, P.J.; Cristea, S.; Ring, A.M.; Maute, R.L.; Volkmer, A.K.; Volkmer, J.-P.; Liu, J.; Lim, J.S.; et al. CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer. *J. Clin. Invest.* **2016**, *126*, 2610–2620, doi:10.1172/JCI81603.
60. Doyle, A.; Martin, W.J.; Funa, K.; Gazdar, A.; Carney, D.; Martin, S.E.; Linnoila, I.; Cuttitta, F.; Mulshine, J.; Bunn, P. Markedly decreased expression of class I histocompatibility antigens, protein, and mRNA in human small-cell lung cancer. *J. Exp. Med.* **1985**, *161*, 1135–1151, doi:10.1084/jem.161.5.1135.
61. Schwendenwein, A.; Megyesfalvi, Z.; Barany, N.; Valko, Z.; Bugyik, E.; Lang, C.; Ferencz, B.; Paku, S.; Lantos, A.; Fillinger, J.; et al. Molecular profiles of small cell lung cancer subtypes: therapeutic implications. *Mol. Ther. - Oncolytics* **2021**, *20*, 470–483, doi:10.1016/j.omto.2021.02.004.
62. Burr, M.L.; Sparbier, C.E.; Chan, K.L.; Chan, Y.-C.; Kersbergen, A.; Lam, E.Y.N.; Azidis-Yates, E.; Vassiliadis, D.; Bell, C.C.; Gilan, O.; et al. An Evolutionarily Conserved Function of Polycomb Silences the MHC Class I Antigen Presentation Pathway and Enables Immune Evasion in Cancer. *Cancer Cell* **2019**, *36*, 385–401.e8, doi:10.1016/j.ccell.2019.08.008.
63. Yazawa, T.; Kamma, H.; Fujiwara, M.; Matsui, M.; Horiguchi, H.; Satoh, H.; Fujimoto, M.; Yokoyama, K.; Ogata, T. Lack of class II transactivator causes severe deficiency of HLA-DR expression in small cell lung cancer. *J. Pathol.* **1999**, *187*, 191–199, doi:10.1002/(SICI)1096-9896(199901)187:2<191::AID-PATH206>3.0.CO;2-3.
64. He, Y.; Rozeboom, L.; Rivard, C.J.; Ellison, K.; Dziadziuszko, R.; Yu, H.; Zhou, C.; Hirsch, F.R. MHC class II expression in lung cancer. *Lung Cancer* **2017**, *112*, 75–80, doi:10.1016/j.lungcan.2017.07.030.
65. Mahadevan, N.R.; Knelson, E.H.; Wolff, J.O.; Vajdi, A.; Saigí, M.; Campisi, M.; Hong, D.; Thai, T.C.; Piel, B.; Han, S.; et al. Intrinsic Immunogenicity of Small Cell Lung Carcinoma Revealed by Its Cellular Plasticity. *Cancer Discov.* **2021**, *11*, 1952–1969, doi:10.1158/2159-8290.CD-20-0913.
66. Galluzzi, L.; Humeau, J.; Buqué, A.; Zitvogel, L.; Kroemer, G. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 725–741, doi:10.1038/s41571-020-0413-z.
67. Petroni, G.; Buqué, A.; Coussens, L.M.; Galluzzi, L. Targeting oncogene and non-oncogene addiction to inflame the tumour microenvironment. *Nat. Rev. Drug Discov.* **2022**, *21*, 440–462, doi:10.1038/s41573-022-00415-5.
68. Rodriguez-Ruiz, M.E.; Vitale, I.; Harrington, K.J.; Melero, I.; Galluzzi, L. Immunological impact of cell death signaling driven by radiation on the tumor microenvironment. *Nat. Immunol.* **2020**, *21*, 120–134, doi:10.1038/s41590-019-0561-4.
69. Chen, Y.; Jin, Y.; Hu, X.; Chen, M. Effect of chemoradiotherapy on the proportion of circulating lymphocyte subsets in patients with limited-stage small cell lung cancer. *Cancer Immunol. Immunother.* **2021**, *70*, 2867–2876, doi:10.1007/s00262-021-02902-x.
70. Xue, Y.; Gao, S.; Gou, J.; Yin, T.; He, H.; Wang, Y.; Zhang, Y.; Tang, X.; Wu, R. Platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors: preclinical and clinical studies and mechanism of action. *Expert Opin. Drug Deliv.* **2021**, *18*, 187–203, doi:10.1080/17425247.2021.1825376.
71. Sen, T.; Rodriguez, B.L.; Chen, L.; Corte, C.M. Della; Morikawa, N.; Fujimoto, J.; Cristea, S.; Nguyen, T.; Diao, L.; Li, L.; et al. Targeting DNA Damage Response Promotes Antitumor Immunity through STING-Mediated T-cell Activation in Small Cell Lung Cancer. *Cancer*

Discov. **2019**, *9*, 646–661, doi:10.1158/2159-8290.CD-18-1020.

72. Hipp, S.; Voynov, V.; Drobits-Handl, B.; Giragossian, C.; Trapani, F.; Nixon, A.E.; Scheer, J.M.; Adam, P.J. A Bispecific DLL3/CD3 IgG-Like T-Cell Engaging Antibody Induces Antitumor Responses in Small Cell Lung Cancer. *Clin. cancer Res. an Off. J. Am. Assoc. Cancer Res.* **2020**, *26*, 5258–5268, doi:10.1158/1078-0432.CCR-20-0926.
73. Zhang, H.; Christensen, C.L.; Dries, R.; Oser, M.G.; Deng, J.; Diskin, B.; Li, F.; Pan, Y.; Zhang, X.; Yin, Y.; et al. CDK7 Inhibition Potentiates Genome Instability Triggering Antitumor Immunity in Small Cell Lung Cancer. *Cancer Cell* **2020**, *37*, 37-54.e9, doi:10.1016/j.ccell.2019.11.003.
74. Ready, N.E.; Ott, P.A.; Hellmann, M.D.; Zugazagoitia, J.; Hann, C.L.; de Braud, F.; Antonia, S.J.; Ascierto, P.A.; Moreno, V.; Atmaca, A.; et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2020**, *15*, 426–435, doi:10.1016/j.jtho.2019.10.004.
75. Reck, M.; Vicente, D.; Ciuleanu, T.; Gettinger, S.; Peters, S.; Horn, L.; Audigier-Valette, C.; Pardo, N.; Juan-Vidal, O.; Cheng, Y.; et al. Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): Results from CheckMate 331. *Ann. Oncol.* **2018**, *29*, x43, doi:10.1093/annonc/mdy511.004.
76. Owonikoko, T.K.; Kim, H.R.; Govindan, R.; Ready, N.; Reck, M.; Peters, S.; Dakhil, S.R.; Navarro, A.; Rodriguez-Cid, J.; Schenker, M.; et al. Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): Results from the double-blind, rando. *Ann. Oncol.* **2019**, *30*, ii77, doi:10.1093/annonc/mdz094.
77. Ardizzoni, A.; Hansen, H.; Dombornowsky, P.; Gamucci, T.; Kaplan, S.; Postmus, P.; Giaccone, G.; Schaefer, B.; Wanders, J.; Verweij, J. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: A phase II study in patients with refractory and sensitive disease. *J. Clin. Oncol.* **1997**, *15*, 2090–2096, doi:10.1200/JCO.1997.15.5.2090.
78. Asai, N.; Ohkuni, Y.; Kaneko, N.; Yamaguchi, E.; Kubo, A. Relapsed small cell lung cancer: treatment options and latest developments. *Ther. Adv. Med. Oncol.* **2014**, *6*, 69–82, doi:10.1177/1758834013517413.
79. Chung, H.C.; Piha-Paul, S.A.; Lopez-Martin, J.; Schellens, J.H.M.; Kao, S.; Miller, W.H.J.; Delord, J.-P.; Gao, B.; Planchard, D.; Gottfried, M.; et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2020**, *15*, 618–627, doi:10.1016/j.jtho.2019.12.109.
80. Goldman, J.W.; Dowlati, A.; Antonia, S.J.; Nemunaitis, J.J.; Butler, M.O.; Segal, N.H.; Smith, P.A.; Weiss, J.; Zandberg, D.P.; Xiao, F.; et al. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). *J. Clin. Oncol.* **2018**, *36*, 8518, doi:10.1200/JCO.2018.36.15_suppl.8518.
81. Bondarenko, I.; Juan-Vidal, O.; Pajkos, G.; Kryzhanivska, A.; Pápai Székely, Z.; Vicente, D.; Vynnychenko, I.O.; Jones, S.; Wang, Y.; Jiang, H.; et al. Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant ED-SCLC from arm A of the phase II BALTIC study. *Ann. Oncol.* **2018**, *29*, viii596, doi:10.1093/annonc/mdy298.001.
82. Pujol, J.-L.; Greillier, L.; Audigier-Valette, C.; Moro-Sibilot, D.; Uwer, L.; Hureauux, J.; Guisier, F.; Carmier, D.; Madelaine, J.; Otto, J.; et al. A Randomized Non-Comparative Phase II Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients With Small Cell Lung Cancer: Results From the IFCT-1603 Trial. *J.*

Thorac. Oncol. **2019**, *14*, 903–913, doi:<https://doi.org/10.1016/j.jtho.2019.01.008>.

83. Arriola, E.; Wheeler, M.; Galea, I.; Cross, N.; Maishman, T.; Hamid, D.; Stanton, L.; Cave, J.; Geldart, T.; Mulatero, C.; et al. Outcome and Biomarker Analysis from a Multicenter Phase 2 Study of Ipilimumab in Combination with Carboplatin and Etoposide as First-Line Therapy for Extensive-Stage SCLC. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2016**, *11*, 1511–1521, doi:[10.1016/j.jtho.2016.05.028](https://doi.org/10.1016/j.jtho.2016.05.028).
84. Reck, M.; Bondarenko, I.; Luft, A.; Serwatowski, P.; Barlesi, F.; Chacko, R.; Sebastian, M.; Lu, H.; Cuillerot, J.-M.; Lynch, T.J. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2013**, *24*, 75–83, doi:[10.1093/annonc/mds213](https://doi.org/10.1093/annonc/mds213).
85. Reck, M.; Luft, A.; Szczesna, A.; Havel, L.; Kim, S.-W.; Akerley, W.; Pietanza, M.C.; Wu, Y.-L.; Zielinski, C.; Thomas, M.; et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2016**, *34*, 3740–3748, doi:[10.1200/JCO.2016.67.6601](https://doi.org/10.1200/JCO.2016.67.6601).
86. Rudin, C.M.; Awad, M.M.; Navarro, A.; Gottfried, M.; Peters, S.; Csőszi, T.; Cheema, P.K.; Rodriguez-Abreu, D.; Wollner, M.; Yang, J.C.-H.; et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2020**, *38*, 2369–2379, doi:[10.1200/JCO.20.00793](https://doi.org/10.1200/JCO.20.00793).
87. Goldman, J.W.; Dvorkin, M.; Chen, Y.; Reinmuth, N.; Hotta, K.; Trukhin, D.; Statsenko, G.; Hochmair, M.J.; Özgüroğlu, M.; Ji, J.H.; et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet. Oncol.* **2021**, *22*, 51–65, doi:[10.1016/S1470-2045\(20\)30539-8](https://doi.org/10.1016/S1470-2045(20)30539-8).
88. Owonikoko, T.K.; Park, K.; Govindan, R.; Ready, N.; Reck, M.; Peters, S.; Dakhil, S.R.; Navarro, A.; Rodríguez-Cid, J.; Schenker, M.; et al. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2021**, *39*, 1349–1359, doi:[10.1200/JCO.20.02212](https://doi.org/10.1200/JCO.20.02212).
89. Nesbit, E.G.; Leal, T.A.; Kruser, T.J. What is the role of radiotherapy for extensive-stage small cell lung cancer in the immunotherapy era? *Transl. Lung Cancer Res.* **2019**, *8*, S153–S162, doi:[10.21037/tlcr.2019.05.01](https://doi.org/10.21037/tlcr.2019.05.01).
90. Higgins, K.A.; Slotman, B.J. What is the role of consolidative thoracic radiotherapy in the era of chemo-immunotherapy for extensive stage small cell lung cancer? *J. Thorac. Dis.* **2020**, *12*, 6308–6310, doi:[10.21037/jtd.2020.03.15](https://doi.org/10.21037/jtd.2020.03.15).
91. Peters, S.; Pujol, J.-L.; Dafni, U.; Dómine, M.; Popat, S.; Reck, M.; Andrade, J.; Becker, A.; Moro-Sibilot, D.; Curioni-Fontecedro, A.; et al. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy - results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2022**, *33*, 67–79, doi:[10.1016/j.annonc.2021.09.011](https://doi.org/10.1016/j.annonc.2021.09.011).
92. Besse, B.; Menis, J.; Bironzo, P.; Gervais, R.; Greillier, L.; Monnet, I.; Livi, L.; Young, R.; Decroisette, C.; Cloarec, N.; et al. LBA85 REACTION: A phase II study of etoposide and cis/carboplatin with or without pembrolizumab in untreated extensive small cell lung cancer. *Ann. Oncol.* **2020**, *31*, S1211–S1212, doi:[10.1016/j.annonc.2020.08.2327](https://doi.org/10.1016/j.annonc.2020.08.2327).
93. Rudin, C.M.; Liu, S. V; Lu, S.; Soo, R.A.; Hong, M.H.; Lee, J.-S.; Bryl, M.; Dumoulin, D.W.; Rittmeyer, A.; Chiu, C.-H.; et al. SKYSCRAPER-02: Primary results of a phase III,

- randomized, double-blind, placebo-controlled study of atezolizumab (atezo) + carboplatin + etoposide (CE) with or without tiragolumab (tira) in patients (pts) with untreated extensive-stage small cell lung ca. *J. Clin. Oncol.* **2022**, *40*, LBA8507–LBA8507, doi:10.1200/JCO.2022.40.17_suppl.LBA8507.
94. Schulze, A.B.; Evers, G.; Kerkhoff, A.; Mohr, M.; Schliemann, C.; Berdel, W.E.; Schmidt, L.H. Future Options of Molecular-Targeted Therapy in Small Cell Lung Cancer. *Cancers (Basel)*. **2019**, *11*, 690, doi:10.3390/CANCERS11050690.
 95. Tanaka, K.; Isse, K.; Fujihira, T.; Takenoyama, M.; Saunders, L.; Bheddah, S.; Nakanishi, Y.; Okamoto, I. Prevalence of Delta-like protein 3 expression in patients with small cell lung cancer. *Lung Cancer* **2018**, *115*, 116–120, doi:10.1016/j.lungcan.2017.11.018.
 96. Sabari, J.K.; Lok, B.H.; Laird, J.H.; Poirier, J.T.; Rudin, C.M. Unravelling the biology of SCLC: Implications for therapy. *Nat. Rev. Clin. Oncol.* **2017**, *14*, 549–561, doi:10.1038/nrclinonc.2017.71.
 97. Furuta, M.; Sakakibara-Konishi, J.; Kikuchi, H.; Yokouchi, H.; Nishihara, H.; Minemura, H.; Harada, M.; Yamazaki, S.; Akie, K.; Fujita, Y.; et al. Analysis of DLL3 and ASCL1 in Surgically Resected Small Cell Lung Cancer (HOT1702). *Oncologist* **2019**, *24*, e1172–e1179, doi:10.1634/theoncologist.2018-0676.
 98. Saunders, L.R.; Bankovich, A.J.; Anderson, W.C.; Aujay, M.A.; Bheddah, S.; Black, K.; Desai, R.; Escarpe, P.A.; Hampl, J.; Laysang, A.; et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. *Sci. Transl. Med.* **2015**, *7*, 302ra136, doi:10.1126/scitranslmed.aac9459.
 99. Rudin, C.M.; Pietanza, M.C.; Bauer, T.M.; Ready, N.; Morgensztern, D.; Glisson, B.S.; Byers, L.A.; Johnson, M.L.; Burris, H.A. 3rd; Robert, F.; et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet. Oncol.* **2017**, *18*, 42–51, doi:10.1016/S1470-2045(16)30565-4.
 100. Morgensztern, D.; Besse, B.; Greillier, L.; Santana-Davila, R.; Ready, N.; Hann, C.L.; Glisson, B.S.; Farago, A.F.; Dowlati, A.; Rudin, C.M.; et al. Efficacy and Safety of Rovalpituzumab Tesirine in Third-Line and Beyond Patients with DLL3-Expressing, Relapsed/Refractory Small-Cell Lung Cancer: Results From the Phase II TRINITY Study. *Clin. Cancer Res. an Off. J. Am. Assoc. Cancer Res.* **2019**, *25*, 6958–6966, doi:10.1158/1078-0432.CCR-19-1133.
 101. Blackhall, F.; Jao, K.; Greillier, L.; Cho, B.C.; Penkov, K.; Reguart, N.; Majem, M.; Nackaerts, K.; Syrigos, K.; Hansen, K.; et al. Efficacy and Safety of Rovalpituzumab Tesirine Compared With Topotecan as Second-Line Therapy in DLL3-High SCLC: Results From the Phase 3 TAHOE Study. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2021**, *16*, 1547–1558, doi:10.1016/j.jtho.2021.02.009.
 102. Johnson, M.L.; Zvirbule, Z.; Laktionov, K.; Helland, A.; Cho, B.C.; Gutierrez, V.; Colinet, B.; Lena, H.; Wolf, M.; Gottfried, M.; et al. Rovalpituzumab Tesirine as a Maintenance Therapy After First-Line Platinum-Based Chemotherapy in Patients With Extensive-Stage-SCLC: Results From the Phase 3 MERU Study. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2021**, *16*, 1570–1581, doi:10.1016/j.jtho.2021.03.012.
 103. Jiang, S.X.; Sato, Y.; Kuwano, S.; Kameya, T. Expression of bcl-2 oncogene protein is prevalent in small cell lung carcinomas. *J. Pathol.* **1995**, *177*, 135–138, doi:10.1002/path.1711770206.
 104. Rudin, C.M.; Salgia, R.; Wang, X.; Hodgson, L.D.; Masters, G.A.; Green, M.; Vokes, E.E. Randomized phase II Study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2008**, *26*, 870–876,

doi:10.1200/JCO.2007.14.3461.

105. Rudin, C.M.; Hann, C.L.; Garon, E.B.; Ribeiro de Oliveira, M.; Bonomi, P.D.; Camidge, D.R.; Chu, Q.; Giaccone, G.; Khaira, D.; Ramalingam, S.S.; et al. Phase II study of single-agent navitoclax (ABT-263) and biomarker correlates in patients with relapsed small cell lung cancer. *Clin. cancer Res. an Off. J. Am. Assoc. Cancer Res.* **2012**, *18*, 3163–3169, doi:10.1158/1078-0432.CCR-11-3090.
106. Lakhani, N.J.; Rasco, D.W.; Zeng, Q.; Tang, Y.; LIANG, Z.; Wang, H.; Lu, M.; Chen, J.; Fu, L.; Wang, C.; et al. First-in-human study of palcitoclax (APG-1252), a novel dual Bcl-2/Bcl-xL inhibitor, demonstrated advantages in platelet safety while maintaining anticancer effect in U.S. patients with metastatic solid tumors. *J. Clin. Oncol.* **2020**, *38*, 3509, doi:10.1200/JCO.2020.38.15_suppl.3509.
107. Jia, D.; Augert, A.; Kim, D.-W.; Eastwood, E.; Wu, N.; Ibrahim, A.H.; Kim, K.-B.; Dunn, C.T.; Pillai, S.P.S.; Gazdar, A.F.; et al. Crebbp Loss Drives Small Cell Lung Cancer and Increases Sensitivity to HDAC Inhibition. *Cancer Discov.* **2018**, *8*, 1422–1437, doi:10.1158/2159-8290.CD-18-0385.
108. Mita, A.; Loeffler, M.; Bui, N.; Remmy, D.; Mehrling, T.; Mita, M.; Rimel, B.J.; Natale, R.B.; Kummar, S. A phase I study of tinostamustine in patients (pts) with advanced solid tumours. *Ann. Oncol.* **2019**, *30*, v177–v178, doi:10.1093/annonc/mdz244.032.
109. Rudin, C.M.; Durinck, S.; Stawiski, E.W.; Poirier, J.T.; Modrusan, Z.; Shames, D.S.; Bergbower, E.A.; Guan, Y.; Shin, J.; Guillory, J.; et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat. Genet.* **2012**, *44*, 1111–1116, doi:10.1038/ng.2405.
110. Weina, K.; Utikal, J. SOX2 and cancer: current research and its implications in the clinic. *Clin. Transl. Med.* **2014**, *3*, 19, doi:10.1186/2001-1326-3-19.
111. Pietanza, M.C.; Litvak, A.M.; Varghese, A.M.; Krug, L.M.; Fleisher, M.; Teitcher, J.B.; Holodny, A.I.; Sima, C.S.; Woo, K.M.; Ng, K.K.; et al. A phase I trial of the Hedgehog inhibitor, sonidegib (LDE225), in combination with etoposide and cisplatin for the initial treatment of extensive stage small cell lung cancer. *Lung Cancer* **2016**, *99*, 23–30, doi:10.1016/j.lungcan.2016.04.014.
112. Belani, C.P.; Dahlberg, S.E.; Rudin, C.M.; Fleisher, M.; Chen, H.X.; Takebe, N.; Velasco, M.R.J.; Tester, W.J.; Sturtz, K.; Hann, C.L.; et al. Vismodegib or cixutumumab in combination with standard chemotherapy for patients with extensive-stage small cell lung cancer: A trial of the ECOG-ACRIN Cancer Research Group (E1508). *Cancer* **2016**, *122*, 2371–2378, doi:10.1002/cncr.30062.
113. Melichar, B.; Adenis, A.; Lockhart, A.C.; Bennouna, J.; Dees, E.C.; Kayaleh, O.; Obermannova, R.; DeMichele, A.; Zatloukal, P.; Zhang, B.; et al. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm p. *Lancet. Oncol.* **2015**, *16*, 395–405, doi:10.1016/S1470-2045(15)70051-3.
114. Owonikoko, T.K.; Niu, H.; Nackaerts, K.; Csoszi, T.; Ostoros, G.; Mark, Z.; Baik, C.; Joy, A.A.; Chouaid, C.; Jaime, J.C.; et al. Randomized Phase II Study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line Therapy for SCLC: Primary and Correlative Biomarker Analyses. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2020**, *15*, 274–287, doi:10.1016/j.jtho.2019.10.013.
115. Tsoukalas, N.; Aravantinou-Fatorou, E.; Baxevanos, P.; Tolia, M.; Tsapakidis, K.; Galanopoulos, M.; Lontos, M.; Kyrgias, G. Advanced small cell lung cancer (SCLC): new challenges and new expectations. *Ann. Transl. Med.* **2018**, *6*, 145, doi:10.21037/atm.2018.03.31.

116. Chalisehar, M.D.; Wait, S.J.; Huang, F.; Ireland, A.S.; Mukhopadhyay, A.; Lee, Y.; Schuman, S.S.; Guthrie, M.R.; Berrett, K.C.; Vahrenkamp, J.M.; et al. MYC-Driven Small-Cell Lung Cancer is Metabolically Distinct and Vulnerable to Arginine Depletion. *Clin. cancer Res. an Off. J. Am. Assoc. Cancer Res.* **2019**, *25*, 5107–5121, doi:10.1158/1078-0432.CCR-18-4140.
117. Huang, Y.-H.; Klingbeil, O.; He, X.-Y.; Wu, X.S.; Arun, G.; Lu, B.; Somerville, T.D.D.; Milazzo, J.P.; Wilkinson, J.E.; Demerdash, O.E.; et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. *Genes Dev.* **2018**, *32*, 915–928, doi:10.1101/gad.314815.118.
118. Wang, Z.; Lu, P.; Liang, Z.; Zhang, Z.; Shi, W.; Cai, X.; Chen, C. Increased insulin-like growth factor 1 receptor (IGF1R) expression in small cell lung cancer and the effect of inhibition of IGF1R expression by RNAi on growth of human small cell lung cancer NCI-H446 cell. *Growth Factors* **2015**, *33*, 337–346, doi:10.3109/08977194.2015.1088533.
119. Ferté, C.; Lorient, Y.; Clémenson, C.; Commo, F.; Gombos, A.; Bibault, J.-E.; Fumagalli, I.; Hamama, S.; Auger, N.; Lahon, B.; et al. IGF-1R targeting increases the antitumor effects of DNA-damaging agents in SCLC model: an opportunity to increase the efficacy of standard therapy. *Mol. Cancer Ther.* **2013**, *12*, 1213–1222, doi:10.1158/1535-7163.MCT-12-1067.
120. Ellis, P.M.; Shepherd, F.A.; Laurie, S.A.; Goss, G.D.; Olivo, M.; Powers, J.; Seymour, L.; Bradbury, P.A. NCIC CTG IND.190 phase I trial of dalotuzumab (MK-0646) in combination with cisplatin and etoposide in extensive-stage small-cell lung cancer. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2014**, *9*, 410–413, doi:10.1097/JTO.0000000000000058.
121. Chiappori, A.A.; Otterson, G.A.; Dowlati, A.; Traynor, A.M.; Horn, L.; Owonikoko, T.K.; Ross, H.J.; Hann, C.L.; Abu Hejleh, T.; Nieva, J.; et al. A Randomized Phase II Study of Linsitinib (OSI-906) Versus Topotecan in Patients With Relapsed Small-Cell Lung Cancer. *Oncologist* **2016**, *21*, 1163–1164, doi:10.1634/theoncologist.2016-0220.
122. Cao, H.; Dong, W.; Shen, H.; Xu, J.; Zhu, L.; Liu, Q.; Du, J. Combinational Therapy Enhances the Effects of Anti-IGF-1R mAb Figitumumab to Target Small Cell Lung Cancer. *PLoS One* **2015**, *10*, e0135844, doi:10.1371/journal.pone.0135844.
123. Byers, L.A.; Wang, J.; Nilsson, M.B.; Fujimoto, J.; Saintigny, P.; Yordy, J.; Giri, U.; Peyton, M.; Fan, Y.H.; Diao, L.; et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. *Cancer Discov.* **2012**, *2*, 798–811, doi:10.1158/2159-8290.CD-12-0112.
124. Woll, P.; Gaunt, P.; Steele, N.; Ahmed, S.; Mulatero, C.; Shah, R.; Danson, S.; Hodgkinson, E.; James, K.; Watkins, B.; et al. P1.07-015 STOMP: A UK National Cancer Research Network Randomised, Double Blind, Multicentre Phase II Trial of Olaparib as Maintenance Therapy in SCLC. *J. Thorac. Oncol.* **2017**, *12*, S704–S705, doi:10.1016/j.jtho.2016.11.926.
125. Woll, P.; Gaunt, P.; Danson, S.; Steele, N.; Ahmed, S.; Mulatero, C.; Shah, R.; Bhosle, J.; Hodgkinson, E.; Watkins, B.; et al. Olaparib as maintenance treatment in patients with chemosensitive small cell lung cancer (STOMP): A randomised, double-blind, placebo-controlled phase II trial. *Lung Cancer* **2022**, *171*, 26–33, doi:10.1016/j.lungcan.2022.07.007.
126. de Bono, J.; Ramanathan, R.K.; Mina, L.; Chugh, R.; Glaspy, J.; Rafii, S.; Kaye, S.; Sachdev, J.; Heymach, J.; Smith, D.C.; et al. Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline BRCA1/2 Mutations and Selected Sporadic Cancers. *Cancer Discov.* **2017**, *7*, 620–629, doi:10.1158/2159-8290.CD-16-1250.
127. Liu, X.; Shi, Y.; Guan, R.; Donawho, C.; Luo, Y.; Palma, J.; Zhu, G.-D.; Johnson, E.F.; Rodriguez, L.E.; Ghoreishi-Haack, N.; et al. Potentiation of temozolomide cytotoxicity by poly(ADP)ribose polymerase inhibitor ABT-888 requires a conversion of single-stranded

DNA damages to double-stranded DNA breaks. *Mol. Cancer Res.* **2008**, *6*, 1621–1629, doi:10.1158/1541-7786.MCR-08-0240.

128. Pietanza, M.C.; Waqar, S.N.; Krug, L.M.; Dowlati, A.; Hann, C.L.; Chiappori, A.; Owonikoko, T.K.; Woo, K.M.; Cardnell, R.J.; Fujimoto, J.; et al. Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2018**, *36*, 2386–2394, doi:10.1200/JCO.2018.77.7672.
129. Ballestrero, A.; Bedognetti, D.; Ferraioli, D.; Franceschelli, P.; Labidi-Galy, S.I.; Leo, E.; Murai, J.; Pommier, Y.; Tsantoulis, P.; Vellone, V.G.; et al. Report on the first SLFN11 monothematic workshop: from function to role as a biomarker in cancer. *J. Transl. Med.* **2017**, *15*, 199.
130. Farago, A.F.; Yeap, B.Y.; Stanzione, M.; Hung, Y.P.; Heist, R.S.; Marcoux, J.P.; Zhong, J.; Rangachari, D.; Barbie, D.A.; Phat, S.; et al. Combination Olaparib and Temozolomide in Relapsed Small-Cell Lung Cancer. *Cancer Discov.* **2019**, *9*, 1372–1387, doi:10.1158/2159-8290.CD-19-0582.
131. Goldman, J.W.; Cummings, A.L.; Mendenhall, M.A.; Velez, M.A.; Babu, S.; Johnson, T.T.; Alcantar, J.M.; Dakhil, S.R.; Kanamori, D.E.; Lawler, W.E.; et al. Primary analysis from the phase 2 study of continuous talazoparib (TALA) plus intermittent low-dose temozolomide (TMZ) in patients with relapsed or refractory extensive-stage small cell lung cancer (ES-SCLC). *J. Clin. Oncol.* **2022**, *40*, 8517, doi:10.1200/JCO.2022.40.16_suppl.8517.
132. Owonikoko, T.K.; Dahlberg, S.E.; Sica, G.L.; Wagner, L.I.; Wade, J.L. 3rd; Srkalovic, G.; Lash, B.W.; Leach, J.W.; Leal, T.B.; Aggarwal, C.; et al. Randomized Phase II Trial of Cisplatin and Etoposide in Combination With Veliparib or Placebo for Extensive-Stage Small-Cell Lung Cancer: ECOG-ACRIN 2511 Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2019**, *37*, 222–229, doi:10.1200/JCO.18.00264.
133. Byers, L.A.; Bentsion, D.; Gans, S.; Penkov, K.; Son, C.; Sibille, A.; Owonikoko, T.K.; Groen, H.J.M.; Gay, C.M.; Fujimoto, J.; et al. Veliparib in Combination with Carboplatin and Etoposide in Patients with Treatment-Naïve Extensive-Stage Small Cell Lung Cancer: A Phase 2 Randomized Study. *Clin. cancer Res. an Off. J. Am. Assoc. Cancer Res.* **2021**, *27*, 3884–3895, doi:10.1158/1078-0432.CCR-20-4259.
134. Ai, X.; Pan, Y.; Shi, J.; Yang, N.; Liu, C.; Zhou, J.; Zhang, X.; Dong, X.; He, J.; Li, X.; et al. Efficacy and Safety of Niraparib as Maintenance Treatment in Patients With Extensive-Stage SCLC After First-Line Chemotherapy: A Randomized, Double-Blind, Phase 3 Study. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2021**, *16*, 1403–1414, doi:10.1016/j.jtho.2021.04.001.
135. Wu, Z.Z.; Zhang, S.J.; Hu, Y. Efficacy of olaparib combined with pembrolizumab in second-line treatment for extensive-stage small cell lung cancer. *Chinese J. Oncol.* **2020**, *42*, 590–593, doi:10.3760/cma.j.cn112152-20200319-00226.
136. Thomas, A.; Vilimas, R.; Trindade, C.; Erwin-Cohen, R.; Roper, N.; Xi, L.; Krishnasamy, V.; Levy, E.; Mammen, A.; Nichols, S.; et al. Durvalumab in Combination with Olaparib in Patients with Relapsed SCLC: Results from a Phase II Study. *J. Thorac. Oncol.* **2019**, *14*, 1447–1457, doi:10.1016/j.jtho.2019.04.026.
137. Shibata, M.; Ham, K.; Hoque, M.O. A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. *Int. J. cancer* **2018**, *143*, 2133–2144, doi:10.1002/ijc.31561.
138. Wang, G.; Lu, X.; Dey, P.; Deng, P.; Wu, C.C.; Jiang, S.; Fang, Z.; Zhao, K.; Konaparthi, R.; Hua, S.; et al. Targeting YAP-Dependent MDSC Infiltration Impairs Tumor Progression. *Cancer Discov.* **2016**, *6*, 80–95, doi:10.1158/2159-8290.CD-15-0224.
139. Horie, M.; Saito, A.; Ohshima, M.; Suzuki, H.I.; Nagase, T. YAP and TAZ modulate cell

- phenotype in a subset of small cell lung cancer. *Cancer Sci.* **2016**, *107*, 1755–1766, doi:10.1111/cas.13078.
140. Tarhini, A.; Kotsakis, A.; Gooding, W.; Shuai, Y.; Petro, D.; Friedland, D.; Belani, C.P.; Dacic, S.; Argiris, A. Phase II study of everolimus (RAD001) in previously treated small cell lung cancer. *Clin. cancer Res. an Off. J. Am. Assoc. Cancer Res.* **2010**, *16*, 5900–5907, doi:10.1158/1078-0432.CCR-10-0802.
141. Sun, J.M.; Kim, J.R.; Do, I.G.; Lee, S.Y.; Lee, J.; Choi, Y.L.; Ahn, J.S.; Ahn, M.J.; Park, K. A phase-1b study of everolimus plus paclitaxel in patients with small-cell lung cancer. *Br. J. Cancer* **2013**, *109*, 1482–1487, doi:10.1038/bjc.2013.467.
142. Besse, B.; Heist, R.S.; Papadimitrakopoulou, V.A.; Camidge, D.R.; Beck, J.T.; Schmid, P.; Mulatero, C.; Miller, N.; Dimitrijevic, S.; Urva, S.; et al. A phase Ib dose-escalation study of everolimus combined with cisplatin and etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2014**, *25*, 505–511, doi:10.1093/annonc/mdt535.
143. McColl, K.; Wildey, G.; Sakre, N.; Lipka, M.B.; Behtaj, M.; Kresak, A.; Chen, Y.; Yang, M.; Velcheti, V.; Fu, P.; et al. Reciprocal expression of INSM1 and YAP1 defines subgroups in small cell lung cancer. *Oncotarget* **2017**, *8*, 73745–73756, doi:10.18632/oncotarget.20572.
144. Salven, P.; Ruotsalainen, T.; Mattson, K.; Joensuu, H. High pre-treatment serum level of vascular endothelial growth factor (VEGF) is associated with poor outcome in small-cell lung cancer. *Int. J. Cancer* **1998**, *79*, 144–146, doi:10.1002/(SICI)1097-0215(19980417)79:2<144::AID-IJC8>3.0.CO;2-T.
145. Fontanini, G.; Faviana, P.; Lucchi, M.; Boldrini, L.; Mussi, A.; Camacci, T.; Mariani, M.A.; Angeletti, C.A.; Basolo, F.; Pingitore, R. A high vascular count and overexpression of vascular endothelial growth factor are associated with unfavourable prognosis in operated small cell lung carcinoma. *Br. J. Cancer* **2002**, *86*, 558–563, doi:10.1038/sj.bjc.6600130.
146. Montanino, A.; Manzo, A.; Carillio, G.; Palumbo, G.; Esposito, G.; Sforza, V.; Costanzo, R.; Sandomenico, C.; Botti, G.; Piccirillo, M.C.; et al. Angiogenesis Inhibitors in Small Cell Lung Cancer. *Front. Oncol.* **2021**, *11*, 655316, doi:10.3389/FONC.2021.655316/FULL.
147. Spigel, D.R.; Townley, P.M.; Waterhouse, D.M.; Fang, L.; Adiguzel, I.; Huang, J.E.; Karlin, D.A.; Faoro, L.; Scappaticci, F.A.; Socinski, M.A. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2011**, *29*, 2215–2222, doi:10.1200/JCO.2010.29.3423.
148. Pujol, J.L.; Lavole, A.; Quoix, E.; Molinier, O.; Souquet, P.J.; Barlesi, F.; Le Caer, H.; Moro-Sibilot, D.; Fournel, P.; Oster, J.P.; et al. Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: Results from the IFCT-0802 trial. *Ann. Oncol.* **2015**, *26*, 908–914, doi:10.1093/annonc/mdv065.
149. Tiseo, M.; Boni, L.; Ambrosio, F.; Camerini, A.; Baldini, E.; Cinieri, S.; Brighenti, M.; Zanelli, F.; Defraia, E.; Chiari, R.; et al. Italian, multicenter, phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small-cell lung cancer: The GOIRC-AIFA FARM6PMFJM trial. *J. Clin. Oncol.* **2017**, *35*, 1281–1287, doi:10.1200/JCO.2016.69.4844.
150. Arnold, A.M.; Seymour, L.; Smylie, M.; Ding, K.; Ung, Y.; Findlay, B.; Lee, C.W.; Djurfeldt, M.; Whitehead, M.; Ellis, P.; et al. Phase II study of vandetanib or placebo in small-cell lung cancer patients after complete or partial response to induction chemotherapy with or without radiation therapy: National Cancer Institute of Canada Clinical Trials Group Study BR.20. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2007**, *25*, 4278–4284, doi:10.1200/JCO.2007.12.3083.

151. Sanborn, R.E.; Patel, J.D.; Masters, G.A.; Jayaram, N.; Stephens, A.; Guarino, M.; Misleh, J.; Wu, J.; Hanna, N. A randomized, double-blind, phase 2 trial of platinum therapy plus etoposide with or without concurrent vandetanib (ZD6474) in patients with previously untreated extensive-stage small cell lung cancer: Hoosier Cancer Research Network LUN06-113. *Cancer* **2017**, *123*, 303–311, doi:10.1002/cncr.30287.
152. Han, J.-Y.; Kim, H.Y.; Lim, K.Y.; Han, J.H.; Lee, Y.J.; Kwak, M.H.; Kim, H.J.; Yun, T.; Kim, H.T.; Lee, J.S. A phase II study of sunitinib in patients with relapsed or refractory small cell lung cancer. *Lung Cancer* **2013**, *79*, 137–142, doi:10.1016/j.lungcan.2012.09.019.
153. Ready, N.E.; Pang, H.H.; Gu, L.; Otterson, G.A.; Thomas, S.P.; Miller, A.A.; Baggstrom, M.; Masters, G.A.; Graziano, S.L.; Crawford, J.; et al. Chemotherapy With or Without Maintenance Sunitinib for Untreated Extensive-Stage Small-Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase II Study-CALGB 30504 (Alliance). *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2015**, *33*, 1660–1665, doi:10.1200/JCO.2014.57.3105.
154. Spigel, D.R.; Greco, F.A.; Rubin, M.S.; Shipley, D.; Thompson, D.S.; Lubiner, E.T.; Eakle, J.F.; Quinn, R.; Burris, H.A.; Hainsworth, J.D. Phase II study of maintenance sunitinib following irinotecan and carboplatin as first-line treatment for patients with extensive-stage small-cell lung cancer. *Lung Cancer* **2012**, *77*, 359–364, doi:10.1016/j.lungcan.2012.03.009.
155. Sharma, N.; Pennell, N.; Nickolich, M.; Halmos, B.; Ma, P.; Mekhail, T.; Fu, P.; Dowlati, A. Phase II trial of sorafenib in conjunction with chemotherapy and as maintenance therapy in extensive-stage small cell lung cancer. *Invest. New Drugs* **2014**, *32*, 362–368, doi:10.1007/s10637-013-0061-6.
156. Cheng, Y.; Wang, Q.; Li, K.; Shi, J.; Liu, Y.; Wu, L.; Han, B.; Chen, G.; He, J.; Wang, J.; et al. Overall survival (OS) update in ALTER 1202: Anlotinib as third-line or further-line treatment in relapsed small-cell lung cancer (SCLC). *Ann. Oncol.* **2019**, *30*, v711, doi:10.1093/annonc/mdz264.002.
157. Xu, Y.; Huang, Z.; Lu, H.; Yu, X.; Li, Y.; Li, W.; Chen, J.; Chen, M.; Gong, L.; Chen, K.; et al. Apatinib in patients with extensive-stage small-cell lung cancer after second-line or third-line chemotherapy: a phase II, single-arm, multicentre, prospective study. *Br. J. Cancer* **2019**, *121*, 640–646, doi:10.1038/s41416-019-0583-6.
158. Liu, Y.; Hu, X.; Jiang, J.; Yang, L.; Zhou, S.; Liu, P.; Li, J.; Wang, Y.; Hao, X.; Shi, Y. A Prospective Study of Apatinib in Patients with Extensive-Stage Small Cell Lung Cancer After Failure of Two or More Lines of Chemotherapy. *Oncologist* **2020**, *25*, e833–e842, doi:10.1634/theoncologist.2019-0391.
159. Fan, Y.; Zhao, J.; Wang, Q.; Huang, D.; Li, X.; Chen, J.; Fang, Y.; Duan, J.; Zhou, C.; Hu, Y.; et al. Camrelizumab Plus Apatinib in Extensive-Stage SCLC (PASSION): A Multicenter, Two-Stage, Phase 2 Trial. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2021**, *16*, 299–309, doi:10.1016/j.jtho.2020.10.002.
160. Santamaría Nuñez, G.; Robles, C.M.G.; Giraudon, C.; Martínez-Leal, J.F.; Compe, E.; Coin, F.; Aviles, P.; Galmarini, C.M.; Egly, J.-M. Lurbinectedin Specifically Triggers the Degradation of Phosphorylated RNA Polymerase II and the Formation of DNA Breaks in Cancer Cells. *Mol. Cancer Ther.* **2016**, *15*, 2399–2412, doi:10.1158/1535-7163.MCT-16-0172.
161. Singh, S.; Jaigirdar, A.A.; Mulkey, F.; Cheng, J.; Hamed, S.S.; Li, Y.; Liu, J.; Zhao, H.; Goheer, A.; Helms, W.S.; et al. FDA Approval Summary: Lurbinectedin for the Treatment of Metastatic Small Cell Lung Cancer. *Clin. cancer Res. an Off. J. Am. Assoc. Cancer Res.* **2021**, *27*, 2378–2382, doi:10.1158/1078-0432.CCR-20-3901.
162. Belgiovine, C.; Bello, E.; Liguori, M.; Craparotta, I.; Mannarino, L.; Paracchini, L.; Beltrame, L.; Marchini, S.; Galmarini, C.M.; Mantovani, A.; et al. Lurbinectedin reduces tumour-

associated macrophages and the inflammatory tumour microenvironment in preclinical models. *Br. J. Cancer* **2017**, *117*, 628–638, doi:10.1038/bjc.2017.205.

163. Trigo, J.; Subbiah, V.; Besse, B.; Moreno, V.; López, R.; Sala, M.A.; Peters, S.; Ponce, S.; Fernández, C.; Alfaro, V.; et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet. Oncol.* **2020**, *21*, 645–654, doi:10.1016/S1470-2045(20)30068-1.
164. Calvo, E.; Moreno, V.; Flynn, M.; Holgado, E.; Olmedo, M.E.; Lopez Criado, M.P.; Kahatt, C.; Lopez-Vilariño, J.A.; Siguero, M.; Fernandez-Teruel, C.; et al. Antitumor activity of lurbinectedin (PM01183) and doxorubicin in relapsed small-cell lung cancer: results from a phase I study. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2017**, *28*, 2559–2566, doi:10.1093/annonc/mdx357.
165. Paz-Ares, L.; Ciuleanu, T.; Navarro, A.; Fulop, A.; Cousin, S.; Bonanno, L.; Smit, E.; Chiappori, A.; Olmedo, M.E.; Horvath, I.; et al. PL02.03 Lurbinectedin/Doxorubicin versus CAV or Topotecan in Relapsed SCLC Patients: Phase III Randomized ATLANTIS Trial. *J. Thorac. Oncol.* **2021**, *16*, S844–S845, doi:https://doi.org/10.1016/j.jtho.2021.08.030.
166. Navarro, A.; Ponce Aix, S.; Barneto - Aranda, I.C.; Smit, E.F.; Lopez-Vilariño, J.A.; Nieto, A.; Kahatt, C.M.; Zeaiter, A.H.; Cousin, S.; Bischoff, H.; et al. Analysis of patients with relapsed small cell lung cancer (SCLC) receiving single-agent lurbinectedin in the phase 3 ATLANTIS trial. *J. Clin. Oncol.* **2022**, *40*, 8524–8524, doi:10.1200/jco.2022.40.16_suppl.8524.
167. Calles, A.; Navarro, A.; Doger, B.; de Miguel, M.J.; Alvarez Alvarez, R.M.; Moreno, V.; Ramón, J.; Galera López, M. del M.; Hernandez-Guerrero, T.; Corral, E.; et al. A phase 1/2 trial of lurbinectedin (L) in combination with pembrolizumab (P) in relapsed small cell lung cancer (SCLC): The LUPER study. *J. Clin. Oncol.* **2022**, *40*, 8581–8581, doi:10.1200/jco.2022.40.16_suppl.8581.

Highlights

- Current therapeutic strategies for SCLC remain limited
- Immune checkpoint inhibitors set a new benchmark for the treatment of SCLC
- Pro-immunogenic or immunosuppressive features of TME modulate sensitivity to ICIs
- Molecular classification of SCLC has opened a new scenario for new treatment options
- Each molecular subtype of SCLC may present specific therapeutic vulnerabilities