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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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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.

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

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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] (Fig. 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

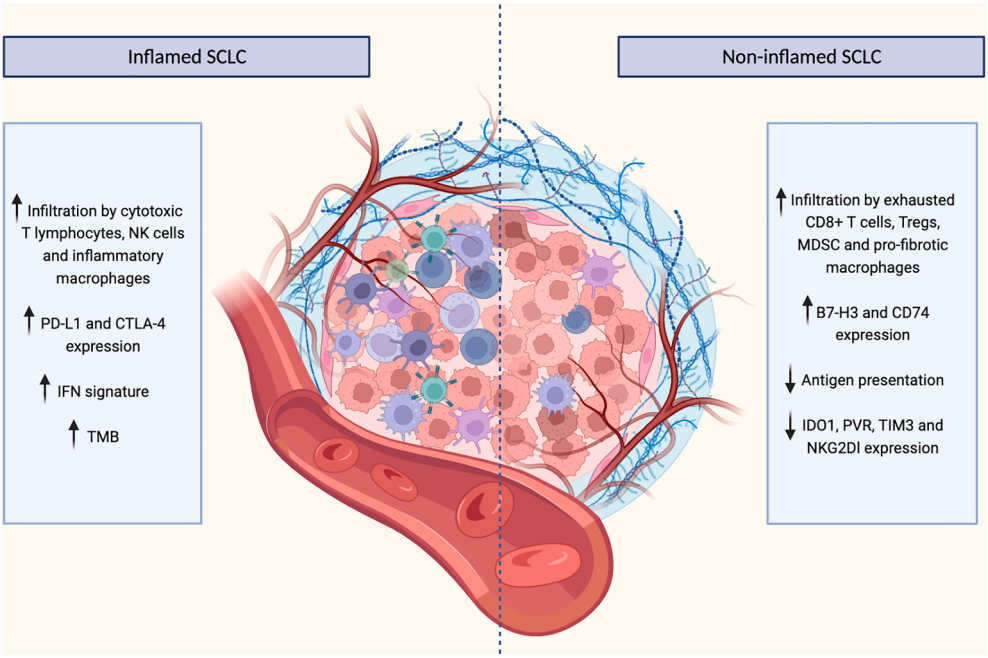

Fig. 1. Features of SCLC predisposing response or resistance to immunotherapy treatment. The different cellular infiltration and characteristics of the tumor microenvironment in SCLC modulate the sensitivity to immunotherapy and can divide SCLC into 'inflamed' or 'non-inflamed' phenotypes according to 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).

[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 β2-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.

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-naive 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 1 shows the main active clinical trials of ICI therapy combined with consolidative thoracic RT for ED-SCLC.

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] (Fig. 2).

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

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.

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

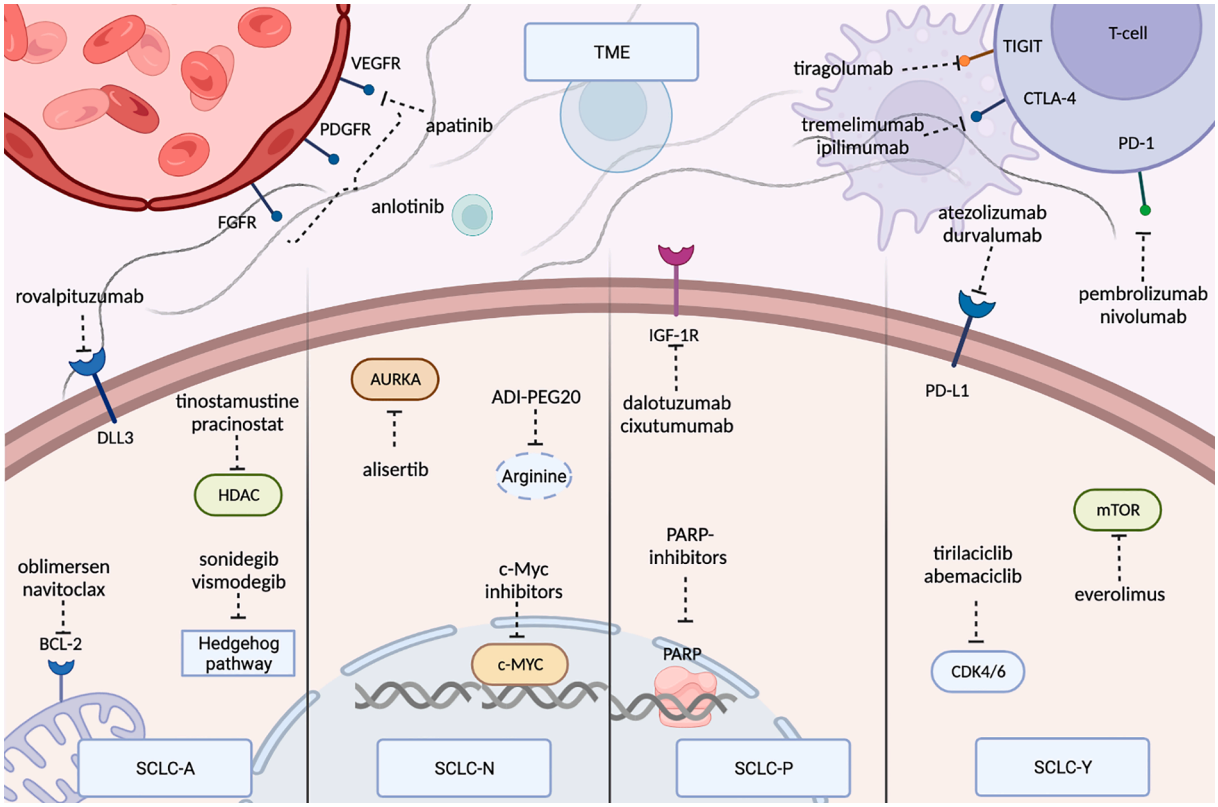

Fig. 2. Potential therapeutic options in SCLC subtypes according to molecular classification. The different expression of key transcription regulators define four different subtypes of SCLC (i.e. SCLC-A, SCLC-N, SCLC-P, SCLC-Y), each of which exhibits a peculiar sensitivity to different therapeutic approaches.

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 [4,109]. 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 [110]. 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 [111].

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 % [112]. 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 [113]. Accordingly, a combination strategy of AURKA and c-MYC inhibitors may improve therapeutic efficacy in this specific subtype [114]. 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 [115].

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 [116–118]. Dalotuzumab, a IGF-1R inhibitor, was tested in a phase I study in combination with CT, showing an ORR of 67 % [119], while the IGF-1R tyrosine kinase inhibitor linsitinib showed no clinical activity in unselected relapsed SCLC patients vs topotecan [120,121]. 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 [111].

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 [122]. When administered as single agents, the PARP-i olaparib and talazoparib showed modest clinical activity [123–125], while the PARP-i veliparib has shown to be active in combination with temozolomide in preclinical study [126]. 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, $p = 0$ 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 [127,128]. More recently, other phase 2 studies demonstrated a benefit of PARP-i olaparib and talazoparib in combination with low-dose TMZ in refractory SCLC [129,130]. 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 [131]. 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 [132]. Another PARP-i, niraparib, as maintenance therapy has recently shown only modest improvement in PFS for patients with platinum-responsive ED-SCLC [133]. 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 [134], while a phase 2 trial of olaparib plus durvalumab suggested that tumor immune phenotypes may be relevant for SCLC responses to ICIs combinations [135].

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 [8,136,137]. 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 [138]. The mTOR inhibitor everolimus was tested as monotherapy in 35 relapsed SCLC patients, but yielded a low rate of disease control (26 %) [139]. 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 % [140], 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 [141]. 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 [138,142].

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

SCLC proliferation has been shown to be closely dependent on microvessels formation. Accordingly, vascular endothelial growth factor (VEGF) is over-expressed in SCLC and is associated with poor prognosis [143,144]. 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 [145]. 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 [146]. 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 [147]. 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) [148]. 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 [149–154]. 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, $p < 0.0029$) [155]. 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 [156,157]. 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 [158].

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 [159,160]. 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 [161]. 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 [162]. 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 [163]. 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 $\geq$ 90 days) and without CNS involvement [164]. 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 [165]. 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) [166].

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.

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