Immunotherapy for small-cell lung cancer: rationale and clinical evidence

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Recent advances in the molecular biology of small cell lung cancer (SCLC) translate into improved outcomes for patients (1-5). This includes rovalpituzumab tesirine (Rova-T), that targets delta-like protein 3 (DLL3). DLL3 is a ligand in the Notch signaling pathway, that is transcriptionally regulated by achaete-scute homolog-1 (ASCL1) and is overexpressed in SCLC (6). In neuroendocrine tumors, Notch action suppresses tumor growth, in contrast to other tumor types in which acts as an oncogenic stimulus. DLL3 is unable to activate the Notch signaling pathway (6). In an early phase clinical trial, patients whose tumors overexpressed DLL3 and received Rova-T as third-line treatment, tumor reduction was achieved in 50% of the patients and 92% experienced at least stabilization of disease (7). In addition, pharmacogenomics approaches to identify drug sensitivity in SCLC (8,9) have shown that DNA repair proteins are overexpressed in SCLC, including poly (ADP-ribose) polymerase 1 (PARP1) (9,10). PARP inhibitors are investigated in patients with SCLC in several clinical trials (11).

The immune system is crucial for the development of SCLC. Paraneoplastic syndromes, common in this disease, are a consequence of an immune imbalance between inhibitory and stimulating mechanisms (12). SCLC patients with paraneoplastic syndromes often have a better prognosis than those without, indicating that the immune system is able to induce an antitumor immune response (13). Immune checkpoint blockade (ICB), either alone or in combination with chemotherapy, represents a particularly promising approach to the treatment of this disease. The combination of ipilimumab, a fully human monoclonal antibody against-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), with etoposide was found to be synergistic in the M109 mouse model of lung cancer (14). Two phase II studies have shown that the combination of phased but not concurrent ipilimumab with paclitaxel and carboplatin improved immune-related progression-free survival (PFS) in chemotherapy-naive non-small cell lung cancer (NSCLC) (15) and extensive-stage disease SCLC (16) patients. However, no improvement in PFS or overall survival (OS) occurred in the SCLC study (16).

Based on the previous preclinical and clinical evidence, the phase III CA184-156 study attempted to evaluate the combination of ipilimumab with first line chemotherapy based on etoposide and platinum versus chemotherapy alone in extensive-stage disease SCLC (17). The study examined the efficacy of ipilimumab administered concurrently with etoposide and platinum versus etoposide and platinum alone. Specifically, patients with chemotherapy naive extensive-stage disease SCLC were randomized at a ratio of one to one to receive either a phased ipilimumab regimen.
(two doses of placebo/etoposide/platinum followed by two doses of ipilimumab/etoposide/platinum and two doses of ipilimumab alone) or a control regimen (four doses of etoposide/platinum followed by two doses of placebo) (17). The primary endpoint was OS. Secondary endpoint was PFS and exploratory endpoints included best overall response rate (ORR), duration of response, survival rate and safety. Median OS was 11.0 months (95% CI, 10.45 to 11.33) in patients treated with chemotherapy plus ipilimumab versus 10.9 months (95% CI, 10.02 to 11.50) in those treated with chemotherapy plus placebo, with 1-year OS rates of 40% in both arms (17). Median PFS was 4.6 months (95% CI, 4.50 to 4.99) in patients treated with chemotherapy plus ipilimumab versus 4.4 months (95% CI, 4.37 to 4.63) in those treated with chemotherapy plus placebo (unstratified log-rank P=0.0161) between arms. Best ORRs were similar in the two arms. Immune-related adverse events were manageable with treatment guidelines (17). The investigators related the lack of benefit of the addition of ipilimumab to two factors: one is that ipilimumab requires a corresponding T-cell activation in the tumor microenvironment in order to have an effective antitumor response and the second is that chemotherapy-induced immunosuppression may be associated with limited T-cell activation and proliferation (17).

The combination of ICB with other conventional or targeted therapies requires deep understanding of the dual functions of interferon-related signaling on the immune system and its non-immune effects (18). During virus infection, virus derived nucleic acids are mainly sensed by certain pattern-recognition receptors (PRRs), such as retinoic acid-inducible gene 1 (RIG1). Binding of RIG1 to its ligand RNAs or short double-stranded RNAs, activates the signaling pathways dependent on the adaptor protein mitochondrial antiviral signaling proteins, leading to induction of the IFN-regulatory factor-3 (IRF-3) and NF-KB-dependent gene expression and the subsequent production of type I and type II IFNs and inflammatory cytokines (19,20). Chemotherapy and radiotherapy activate PRRs, which are critical for INF-I production, priming of T-cells and enhancement of ICB (18). Tumor material can act as damage-associated molecular patterns (DAMPs), that are engaged on dendritic cells and/or tumor-associated macrophages to finally augment IFN-I production and contribute to immune-mediated regression of irradiated or chemotherapy-treated tumors (18). However, when the INF-I signaling persists, it switches from immune stimulatory to immune suppressive. Persistent INF promotes expression of suppressive factors such as PD-L1. Interestingly, nivolumab [a fully human IgG4 programmed cell death protein 1 (PD-1) inhibitor antibody] monotherapy and nivolumab plus ipilimumab have shown antitumor activity with durable responses and manageable safety profiles in previously treated patients with SCLC (21). In a phase II study, the objective response was 55% for advanced non-squamous NSCLC patients treated with the combination of pembrolizumab (a humanized, monoclonal antibody against PD-1), carboplatin, and pemtrexed compared to 29% for those treated with chemotherapy alone (P=0.0016) (22). On the other hand, elevated expression of PRRs and INF-stimulated genes has also immune-independent effects and through stromal fibroblasts and cell exosomes leads to chemotherapy resistance (18).

The CA184-156 study is the largest phase III randomized trial conducted to date in a population of patients with extensive-stage disease SCLC (17). Currently many studies of immunotherapy are ongoing in SCLC (Table 1). The expression of PD-L1 on tumor cells, which is maybe until now the only predictive biomarker for ICB, is rarely found in SCLC cases, though PD-L1 can be expressed in tumor infiltrating macrophages. Stromal expression of PD-L1 can be a biomarker of response to immunotherapy (23). Unraveling the complexities of INF signaling with its immune-stimulatory and suppressive effects, and its immune-independent effects will pave the way for efficient ICB and chemotherapy combinations.
Table 1 Ongoing immunotherapy clinical trials in SCLC

<table>
<thead>
<tr>
<th>Clinical trial identifier</th>
<th>Phase</th>
<th>Summary</th>
<th>Patient population</th>
<th>Primary outcome</th>
<th>Sponsor</th>
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<tr>
<td>PD-1 antibodies</td>
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<tr>
<td>NCT02359019</td>
<td>II</td>
<td>Pembrolizumab after completion of platinum-based chemotherapy</td>
<td>ED-SCLC</td>
<td>PFS</td>
<td>Barbara Ann Karmanos Cancer Institute</td>
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<tr>
<td>NCT02481830</td>
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<td>Nivolumab versus topotecan versus amrubicin (CheckMate 331)</td>
<td>Relapsed SCLC</td>
<td>OS</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>NCT02551432</td>
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<td>Pembrolizumab and paclitaxel</td>
<td>Refractory SCLC</td>
<td>RR</td>
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<td>NCT02402920</td>
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<td>Pembrolizumab and chemotherapy with or without pembrolizumab</td>
<td>LD-SCLC and ED-SCLC</td>
<td>MTD</td>
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<td>PFS</td>
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<td>NCT02934503</td>
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<td>Dynamic changes in PD-L1 expression</td>
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<td>NCT02538666</td>
<td>III</td>
<td>Nivolumab versus nivolumab plus ipilimumab versus placebo after completion of platinum-based chemotherapy (CheckMate 451)</td>
<td>ED-SCLC</td>
<td>OS, PFS</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>NCT02046733</td>
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<td>Nivolumab plus ipilimumab (STIMULI)</td>
<td>LD-SCLC</td>
<td>OS, PFS</td>
<td>ETOP</td>
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<td>Other immunological agents</td>
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<td>NCT02200081</td>
<td>II</td>
<td>MGN1703 (TLR-9 antagonist), maintenance (IMPULSE)</td>
<td>ED-SCLC</td>
<td>OS</td>
<td>Mologen AG</td>
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<td>NCT00483509</td>
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<td>NGR-hTNF plus doxorubicin</td>
<td>Advanced or Metastatic SCLC</td>
<td>PFS</td>
<td>MolMed S.p.A</td>
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</table>

SCLC, small cell lung cancer; ED-SCLC, extensive-stage disease SCLC; LD-SCLC, limited-stage disease SCLC; PFS, progression-free survival; OS or overall survival; EORTC, European Organization for Research and Treatment of Cancer; ETOP, European Thoracic Oncology Platform; NGR-hTNF, asparagine-glycine-arginine-human tumor necrosis factor.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


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