Review

Recent Advances and Future Strategies for Immune-Checkpoint Inhibition in Small-Cell Lung Cancer

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Abstract

Small-cell lung cancer (SCLC) is distinguished from non–small-cell lung cancer by its rapid growth and more frequent metastases. Although patients with SCLC are highly responsive to chemotherapy and radiation therapy, long-term prognosis remains poor, with relapse and disease recurrence occurring in almost all cases. Whereas combination chemotherapies continue to be the standard of care in extensive-stage SCLC, there is value in exploring whether immune-checkpoint inhibition is an effective treatment strategy, given the durable responses in non–small-cell lung cancer. Data from SCLC trials have shown clinical activity and response to cytotoxic T-lymphocyte antigen-4 protein and programmed cell death-1 blockade, suggesting that antibodies targeting these pathways may be effective in improving survival outcome. However, data on clinical activity by programmed cell death-1 ligand expression in SCLC are not widely available. Limited data indicate that programmed cell death-1 ligand expression may not be an ideal biomarker for patient selection. Continued research is necessary to better optimize patient selection and response to therapy.

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Introduction

Small-cell lung cancer (SCLC) accounts for 10%-15% of lung cancers in the United States, with a 5-year survival rate for early-stage and late-stage cancer ranging from 19%-31% and 2%-8%, respectively.[1] SCLC is characterized by rapid growth, early development of metastases, and occurrence almost exclusively in smokers, as compared with non–small-cell lung cancer (NSCLC). As a result, the aggressive nature of the disease often limits surgical benefit. SCLC is often divided into 2 categories: limited and extensive stage.[2] Patients with limited stage disease must have disease that may be encompassed within 1 radiation field, with the disease often localized on 1 side of the chest, whereas patients with extensive stage disease have cancers that have spread throughout and/or outside the lung. Among SCLC patients at the time of diagnosis, approximately 2 of 3 patients are found to have extensive stage disease, with 5-year survival rates typically ranging from 1%-3%.[3]

Treatment options for SCLC include chemotherapy, radiation therapy, and rarely, surgical resection, with treatment strategies typically determined based on cancer stage. Patients with limited stage disease may be treated with radiation therapy directed at the site of the cancer in the chest, combined with chemotherapy, whereas patients with extensive disease may be treated with chemotherapy alone. Patients with limited-stage SCLC who achieve complete response undergo prophylactic cranial irradiation and data for patients with extensive stage disease with response to therapy are likely to benefit as well.[4,5] Surgery is generally only beneficial in approximately 1% of patients.[6]

Patients with SCLC typically present with metastatic disease, and therefore, systemic chemotherapy is the most common treatment strategy. Initial positive responses occur with first-line chemotherapy treatment in both limited and extensive stage patients. However, long-term prognosis remains poor owing to rapid

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development of resistance to chemotherapy, resulting in poor outcomes.[7] Whereas initial response to chemotherapy is approximately 80% in extensive stage SCLC, the median overall survival (OS) remains between 8 and 12 months.[3,8,9]

Improved responses to chemotherapy have been explored, with several approaches including higher-dose or alternative scheduling strategies, but no significant improvements in patient outcomes have been observed. Although combination chemotherapies continue to be the current standard of care for patients with extensive stage SCLC, poor treatment outcomes reinforce the need for novel, alternative treatment strategies to improve OS. Currently, several investigational treatment approaches are being studied, including angiogenesis inhibition, vascular endothelial growth factor (VEGF) inhibition, molecularly targeted therapies, and immunotherapies. Given that durable responses to immune-checkpoint inhibition have been observed in multiple solid tumors, including melanoma, renal cell cancer (RCC), and NSCLC, there is value in exploring whether similar responses to immunotherapy are also observed in SCLC.[10,11]

Cancer immunotherapies aim to stimulate immune responses, thereby inhibiting the tumor from escaping immune surveillance. Two well-characterized checkpoint pathways include the cytotoxic T-lymphocyte antigen-4 protein (CTLA-4) and programmed cell death-1 protein receptor (PD-1) and ligand (PD-L1) pathways. The CTLA-4 checkpoint pathway plays an important role in regulating early T-cell activity peripherally in lymph tissue, whereas the PD-1/PD-L1 checkpoint pathway is involved in suppressing autoimmunity during T-cell activation, allowing for immune tolerance of PD-L1 expressed cells at the site of the tumor.[12] Overexpression of PD-L1 is adopted by multiple solid tumor types, thereby allowing tumor avoidance of immunologic surveillance and promoting cancer growth. Recent advances in the field of immunotherapy, especially with immune-checkpoint inhibition of advanced NSCLC, have led to the development of therapeutic antibodies targeting the CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (atezolizumab/MPDL3280A, durvalumab/MEDI4736, BMS-936559) pathways.

Targeted immunotherapies involving the CTLA-4 and PD-1/PD-L1 checkpoint pathways have shown promise as effective and safe therapies in patients with melanoma, RCC, and NSCLC, as demonstrated by durable responses with respect to objective responses and OS.[10] For example, in a recent phase I dose-escalation trial for patients with advanced melanoma, objective response rates (ORRs) were observed in 61% (95% confidence interval [CI], 49%-72%) of patients receiving nivolumab plus ipilimumab combination therapy compared with 11% (95% CI, 3%-25%) of patients receiving ipilimumab monotherapy.[13] The combination therapy resulted in a considerably higher ORR and frequency of complete response, as well as significantly longer progression-free survival (PFS) when compared with the ipilimumab monotherapy ($P < .001$).[13]

Although many patients respond well to immune checkpoint blockade, there are still patients who do not respond or who progress while on immunotherapy. Therefore, a continued goal is to improve patient selection for optimal response to immunotherapy. The utility of PD-L1 expression as a biomarker has varied in different clinical trials in NSCLC, with some patients who are negative based on PD-L1 immunohistochemistry (IHC) responding to treatment.[14] PD-L1 is also complicated by expression that is influenced by a dynamic tumor microenvironment. For this reason, identification of an ideal biomarker for patient selection is necessary in order to administer treatment preferentially to patients who would preferentially benefit from immunotherapy treatment, thereby limiting exposure to patients for whom the therapy will be ineffective or potentially result in adverse responses.[15]

In this review, we critically evaluate the results from PD-1/PD-L1 and CTLA-4 blockade therapy in SCLC trials. Furthermore, we provide an updated perspective on PD-1/PD-L1 expression, as assessed with IHC, as a predictive biomarker for patient selection, and discuss potential alternative markers for immune checkpoint-directed therapies in SCLC.

Immune-Checkpoint Inhibitory Antibodies

Trial Data Outside SCLC

Early evidence in support of immune-checkpoint inhibition therapy has been demonstrated in NSCLC trials investigating CTLA-4 and PD-1/PD-L1 inhibitory antibodies.

CTLA-4 Inhibitory Antibodies

CTLA-4 inhibitory agents include the monoclonal antibodies, ipilimumab and tremelimumab. Early clinical studies have demonstrated durable responses in multiple tumor types, with phase III trials reporting ipilimumab as the first agent to significantly improve OS in metastatic melanoma.[8] Based on promising results in previous trials in metastatic melanoma, tremelimumab is also currently under study in advanced trials.

PD-1 Inhibitory Antibodies

PD-1 inhibitory agents include nivolumab and pembrolizumab, both monoclonal antibodies approved for treatment of unresectable or metastatic melanoma. Nivolumab and pembrolizumab have additionally been approved for treatment of advanced squamous and non-squamous NSCLC with progression on or after platinum-based chemotherapy. Additionally, nivolumab has been approved for treatment of advanced RCC in patients who have failed previous anti-angiogenic therapy. Recently, nivolumab was also approved for patients with Hodgkin lymphoma who have relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin.

Early results from phase I dose-escalating trials among different tumor types strengthened support for nivolumab.[10,16,17] Among the NSCLC cohort, the ORR was 17% with a median duration of response of 17.1 months, whereas the median OS among patients was 9.9 months. Nivolumab was approved for treatment of advanced squamous NSCLC based on results from phase II (CheckMate 063) and phase III (CheckMate 017) trials. In the phase II study, the observed ORR was 15% (95% CI, 9%-22%), with durable responses of 6 months or longer observed in 59% of patients.[18] Among the cohort, the median OS was 8.2 months (95% CI, 6-11 months), and the OS rate was 41% (95% CI, 32%-50%) at 1 year.[19] In the phase III study, the median OS for nivolumab monotherapy was 9.2 months (95% CI, 7.3-13.3 months) for the nivolumab arm and 6.0 months (95% CI, 5.1-7.3 months) for the docetaxel arm, with an OS hazard ratio