Review

The Evolving Role of Nivolumab in Non–Small-Cell Lung Cancer for Second-Line Treatment: A New Cornerstone for Our Treatment Algorithms. Results From an International Experts Panel Meeting of the Italian Association of Thoracic Oncology

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Abstract

Lung cancer is the leading cause of death from cancer worldwide that currently has only a few available treatment options in patients with no driver mutations. The therapeutic options for patients with non–small-cell lung cancer (NSCLC) who progress after first-line chemotherapy have been limited from a long time. Docetaxel has remained a cornerstone of second-line treatment for more than 20 years, but it is associated with an unfavorable safety profile. Recently, the results from immunotherapy treatment with anti-PD1 and PD-L1 inhibitors has changed our current knowledge base and increased therapeutic options for patients with NSCLC in the second-line setting. The results of 2 randomized phase III trials assessing nivolumab in lung cancer, Check-Mate-017 and Check-Mate-057, have deeply changed our current clinical practice and raised several discussion points. This paper explores the recent findings about nivolumab for the treatment of NSCLC in the second-line setting by analyzing recent trial findings and discussing their implications in clinical practice and future directions. The paper also summarizes the conclusions from an International Experts Panel Meeting of the Italian Association of Thoracic Oncology.

Clinical Lung Cancer, Vol. ■, No. ■, ■-■
Keywords: Anti-PD-1 antibody, Immunotherapy, Nivolumab, PD-L1, Second-line treatment

Introduction

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer-specific death in the US and Europe. In up to 60% of cases, NSCLC is diagnosed at locally advanced or metastatic stages, with a 5-year survival rate of about 5%.[1] Although patients with molecular drivers typically exhibit improved overall survival (OS) and quality-of-life through the use of targeted agents, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)[2-6] and anaplastic lymphoma kinase (ALK) inhibitors,[7-9] for patients with wild-type status, very few therapeutic options are currently available, and OS remains poor. For patients with non-squamous histology and wild-type status, docetaxel, pemetrexed, and erlotinib are currently approved worldwide as second-line treatment after first-line platinum doublet failure,[10] while in squamous NSCLC, only docetaxel and erlotinib are approved. In recent years, the combination of docetaxel with new antiangiogenic agents, such as nintedanib or ramucirumab, has led to improved survival compared with the single agent docetaxel; however, some concerns remain with regard to the safety profile of these combinations. Therefore, based on the results to date, the use of immune checkpoint inhibitors provides a potential scenario that could radically change the treatment algorithm.[11-13]

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Submitted: Sep 23, 2015; Revised: Jan 13, 2016; Accepted: Jan 19, 2016

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1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.cllc.2016.01.004

Evidence to date regarding cancer biology has shown that the interaction between programmed death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) is a key point of cancer homeostasis and immune regulation. PD-1 is expressed on activated T-cells, and the binding of PD-1 to its ligand PD-L1 results in the suppression of the immune response. Cancer evades host immune surveillance by using immune checkpoints, which are inhibitory pathways crucial for maintaining self-tolerance.[14,15] Cancer cells heterogeneously express different promotion and inhibitory ligands that interact with multiple molecules, and surrounding tumor-infiltrating lymphocytes (TIL) express a variety of inhibitory receptors.[14] The inhibitory receptors cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1[16] are the most studied immune checkpoint receptors to date. Importantly, an immunosuppressive tumor microenvironment and the activation of an immune response are driven by the interaction between PD-1 and PD-L1.

PD-L1 is expressed in different cancer types, including NSCLC, and its interaction with PD-1 plays an important role in the blockade of the "cancer immunity cycle."[20] The PD-1 receptor is a member of the immunoglobulin B7-CD28 family and is expressed on TILs, natural killer T-cells, mononuclear cells, and dendritic cells. Recently, various clinical trials exploring the use of anti-PD-1 antibody and PD-L1 inhibitor have shown improved survival and response rates in patients with lung cancer. Therefore, the use of immune checkpoint inhibitors is opening a big break in the progress of lung cancer treatment, moving us into a new era of cancer treatment.[15,17-19]

To date, several immune checkpoints inhibitors, including atezolizumab, durvalumab, nivolumab, and pembrolizumab, are under evaluation in different settings and histology subtypes of lung cancer.[20-22] Nivolumab binds PD-1 with high affinity and blocks its interactions with both B7-H1 and B7-DC.[23] It was initially evaluated in a first-in-human phase I study, in which patients with advanced stage solid tumors were treated with a single dose of nivolumab at 0.3, 1, 3, or 10 mg/kg.[24] Nivolumab was found to be well-tolerated, and dose-limiting toxicities as well as the maximum tolerable dose were not reached. Of the NSCLC patients enrolled in the study, 12 of 39 patients achieved a response, thus confirming the activity of nivolumab in this tumor type.

In a subsequent dose escalation phase Ib study of nivolumab, patients with different solid tumors, including NSCLC, were enrolled.[25] The NSCLC cohort included 129 heavily pretreated patients, whereby 54% had received at least 3 prior lines of therapy. The overall response rate (ORR) was 17% with a median duration of response of 74 weeks (range, 6.1-133.9 weeks). In 8 of 15 (57%) patients, a persistent response greater than 24 weeks was achieved. In addition, 2 patients showed a sustained response of more than 1 year. In 5 patients with non-squamous tumors that did not achieve a response, stable disease was prolonged for more than 24 weeks. For patients treated in the 3 mg/kg cohort, the median OS was 14.9 months with a 1-year OS of 56% and 2-year OS of 45%.[26,27]

Nivolumab has also been evaluated in the CheckMate-063 trial, which was designed as a phase II single-arm, open-label trial that included squamous NSCLC patients who had progressed after 2 or more lines of therapy. The ORR was 14.5%, and responses were achieved across all subgroups. Median time to response was 3.3 months, median progression-free survival (PFS) was 1.9 months, and median OS was 8.2 months. PD-L1 expression was assessed on pre-treatment archival tumor samples from 88% of patients, and 33% of the samples were found to be positive ($\geq$ 5% expression). Responses occurred more frequently in PD-L1-positive tumors, but the difference in ORR between PD-L1-positive versus PD-L1-negative patients was not statistically significant.[28]

Data From Phase III Trials Comparing Nivolumab With Standard Chemotherapy in Second-Line

Squamous NSCLC (Check-Mate 017 Trial)

The Check-Mate-017 trial was designed as a phase III, open-label randomized trial evaluating the efficacy and safety of nivolumab compared with docetaxel in patients with squamous NSCLC progressing during or after first-line platinum-based chemotherapy. In this trial, 272 patients were randomized to receive nivolumab at a dose of 3 mg/kg every 2 weeks or docetaxel at a dose of 75 mg/m^2 every 3 weeks. OS was the primary endpoint, while secondary endpoints included ORR, PFS, safety, and outcomes by PD-L1 expression. In this trial, PD-L1 protein expression was evaluated retrospectively based on pre-treatment (recent or archival) tissue by immunohistochemistry. Of the study population, 83% of the patients were evaluable for PD-L1 expression. Across the pre-specified expression level cut-offs ($\geq$ 1%, $\geq$ 5%, and $\geq$ 10%; Table 1), PD-L1 expression was not prognostic or predictive of any of the efficacy endpoints. However, the results showed a highly statistically significant improvement in OS for patients receiving nivolumab (median, 9.2 vs. 6.0 months, respectively; hazard ratio [HR], 0.59; $P < .001$). Moreover, the results confirmed the superiority of nivolumab for all predefined endpoints, including PFS (3.5 vs. 2.8 months, respectively; HR, 0.62; $P < .001$) and ORR (20% vs. 9%, respectively; $P = .008$). In addition to these clear and robust data, the data for 1-year OS and duration of response also confirmed the superiority of nivolumab. Indeed, the 1-year OS was 42% for patients treated with nivolumab versus 24% for patients receiving docetaxel, and the duration of response was "not yet reached" versus 8.4 months, respectively. In the overall study population, the incidence of grade 3/4 adverse events (AEs) was 6.9% for patients receiving nivolumab versus 55% for the docetaxel treatment arm. No treatment-related deaths were reported for patients treated with nivolumab. All-grade AEs occurred in 58% and 86% of patients in the nivolumab and docetaxel arms, respectively. Overall, 3.1% of patients in the nivolumab arm discontinued treatment due to an AE compared with 10.1% for docetaxel. The most frequently reported ($\geq$ 3% of patients) treatment-related select AEs of any grade were hypothyroidism (4% vs. 0%), diarrhea (8% vs. 20%), and pneumonitis (5% vs. 0%) for nivolumab and docetaxel, respectively.[22] These results confirm that nivolumab is the new cornerstone for second-line treatment of patients with squamous NSCLC and exhibits high efficacy and low toxicity.

Non-Squamous NSCLC (Check-Mate 057 Trial)

In addition to the trial assessing the use of nivolumab in patients with squamous histology, data regarding nivolumab as a second-line treatment for non-squamous NSCLC patients have been reported. In this study, 582 patients were enrolled who had progressed to