

# Nivolumab: first immunotherapy approved for lung cancer

See Commentary on page 310

**T**he approval of nivolumab in early 2015 by the US Food and Drug Administration (FDA) for the treatment of squamous cell non-small-cell lung cancer (NSCLC) marks a second approval for this drug, following a 2014 approval for metastatic melanoma. Approved 3 months ahead of schedule, nivolumab is the first immunotherapy to be approved for the treatment of lung cancer. The drug can help to reinstate the antitumor immune response by targeting the programmed cell death-1 (PD-1) receptor, an “immune checkpoint” protein found on the surface of activated T cells that is involved in inhibiting T-cell activity.

The approval was based on the phase 3, randomized, open-label, international CheckMate017 study (NCT01642004) that was carried out between October 2012 and December 2013 and which was stopped early after nivolumab demonstrated a significant survival benefit. Patients with squamous cell NSCLC with progression on or after platinum-based chemotherapy (n = 272) were randomized 1:1 to receive intravenous nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m<sup>2</sup> every 3 weeks) until disease progression or discontinuation of therapy. Randomization was stratified according to prior paclitaxel therapy and geographic region (US-Canada or Europe or the rest of the world).

Patients who were eligible for the study were aged 18 years or older, had stage IIIB or IV squamous cell NSCLC, disease recurrence after 1 prior platinum-containing regimen, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, and a pretreatment tumor tissue specimen available for biomarker analyses. Patients who had treated stable brain metastases and had received prior maintenance therapy, including epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, were also eligible for enrollment. Those with autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior therapy with T-cell co-stimulation or checkpoint inhibitors, prior docetaxel therapy, and more than 1 prior therapy for metastatic disease, were ineligible for the study.

The primary endpoint was overall survival (OS), and patients were followed continuously during treatment and then every 3 months after discontinuation of treatment. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at week

## What's new, what's important

Earlier this year, the FDA approved nivolumab for the treatment of patients with metastatic squamous non-small-cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including antitumor immune response.

In a large, landmark study, nivolumab demonstrated a statistically significant improvement in OS compared with docetaxel at the protocol prespecified interim analysis. Median OS was 9.2 months (95% CI, 7.3, 13.3) for patients assigned to nivolumab, and 6 months (95% CI, 5.1, 7.3) for those assigned to docetaxel (HR, 0.59; 95% CI, 0.44, 0.79; *P* = .00025). Patients in the study group (n = 117) received nivolumab, 3 mg/kg intravenously every 2 weeks.

The most common adverse reactions among the patients receiving nivolumab were fatigue, dyspnea, musculoskeletal pain, decreased appetite, and cough. The most frequent grade 3 and 4 adverse drug reactions observed in at least 5% of patients treated with nivolumab were dyspnea, fatigue, and musculoskeletal pain. Clinically significant immune-mediated adverse reactions included pneumonitis, colitis, hepatitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism.

The recommended dose of nivolumab is 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. This is an encouraging time for patients with NSCLC, and future trials will refine the role of nivolumab in the management lung cancer and other cancers. ClinicalTrials.gov has listed almost 30 open trials with nivolumab in lung cancer. For more information, go to <https://clinicaltrials.gov/ct2/results?term=Nivolumab+and+lun+g+cancer&recr=Open>.

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9 and every 6 weeks thereafter. Patient-reported outcomes were evaluated using Lung Cancer Symptom Scale and European Quality of Life-5 Dimensions questionnaire. PD-1 ligand (PD-L1) protein expression was analyzed retrospectively in pretreatment tumor biopsy specimens using the Dako automated immunohistochemical assay and samples were considered positive when 1%, 5%, or 10% of cells

## Mechanism of action – nivolumab

### Targeting immune checkpoints to reinstate the antitumor immune response

The immune system has long been thought to have potential in fighting cancer, and immunotherapies that are designed to indirectly kill cancer cells by boosting the host immune response have been developed. Historically, they have proven relatively ineffective, largely because cancer cells have evolved mechanisms to evade the immune system. With an increasing understanding of the ways in which cancer cells achieve this goal came the development of novel immunotherapies that specifically target these immunosuppressive mechanisms.

Nivolumab is an immune checkpoint inhibitor. Immune checkpoints are inhibitory pathways that play an important role in regulating the duration and amplitude of the immune response. These pathways have emerged as an important means by which tumors are able to evade the immune response mounted against them to survive.

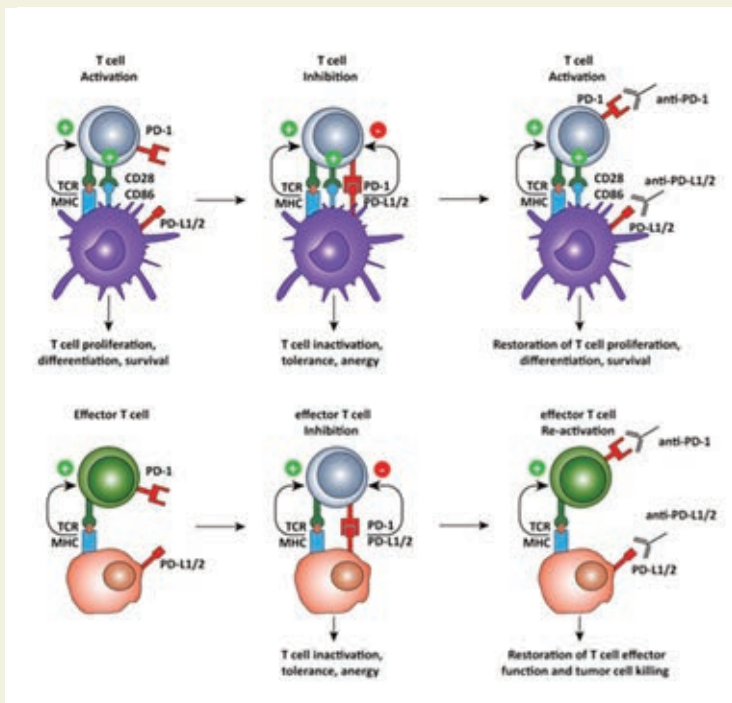
The activation of the cytotoxic T cells of the immune system is a two-step process that requires recognition of an antigen followed by production of an antigen-independent co-regulatory signal that determines whether T cells are activated or inhibited. Immune checkpoints mediate this

second step, essentially acting as an on/off switch for the T cell.

More specifically, nivolumab is a fully human immunoglobulin G4 monoclonal antibody that targets the programmed cell death-1 (PD-1) receptor found on the surface of activated T cells. When bound by its ligands, PD-L1 and PD-L2, the receptor triggers a signaling network that ultimately switches off the T cell and results in a state called T-cell exhaustion, in which the T cells have reduced effector function even in the presence of antigen.

Under normal circumstances, PD-1 and other immune checkpoints serve as the immune system's fail-safe, making sure that the immune response is switched off at the appropriate time, to prevent damage to healthy tissue and to ensure that the host doesn't become self-tolerant. Tumor cells hijack these pathways by overexpressing ligands such as PD-L1 on their surface, which allows them to

deactivate tumor-infiltrating T cells, to inhibit the antitumor immune response. Antibodies such as nivolumab help to keep the T cells switched on so that they are able to eliminate the tumor cells detected by the immune system.



in the tumor membrane were stained in a section including at least 100 evaluable tumor cells.

Demographic and clinical characteristics were generally well balanced across the study population, with a slight imbalance in sex (most patients were men), age (imbalance in patients aged  $\geq 75$  years), and ECOG performance (ECOG of 1). Over a minimum follow-up of 11 months, a median of 8 doses of nivolumab and 3 doses of docetaxel were administered. At least 1 dose delay occurred in 37% of patients in the nivolumab group, with the majority experiencing only 1 delay of 4-7 days that was attributable to personal or administrative reasons, disease progression, or administration of radiation therapy.

Patients in the nivolumab group experienced a >40%

reduction in the risk of death; median OS was 9.2 months, compared with 6 months in the docetaxel arm (hazard ratio [HR], 0.59;  $P < .001$ ). This survival advantage was observed across all prespecified subgroups, except the rest-of-the-world geographic region and patients who were aged 75 years or older. Median progression-free survival (PFS) was 3.5 months in the nivolumab arm, compared with 2.8 months in the docetaxel arm (HR for death or disease progression, 0.62;  $P < .001$ ) and the 1-year PFS rates for each group were 21% and 6%, respectively.

The rate of confirmed objective responses was 20% in patients treated with nivolumab, compared with 9% in those treated with docetaxel ( $P = .008$ ). Median time to response was similar in both groups (2.2 and 2.1 months),

## How I treat NSCLC

Lung cancer is highly prevalent in our community. Many of our patients have multiple comorbidities, are elderly with frail status, have borderline organ functions, and are a challenging population to treat. As with any patient for whom one is considering using systemic anticancer therapy in the setting of advanced disease, it is paramount to assess the patient's performance status, comorbidities, personal values, and goals of therapy before embarking on treatment. Many of the therapeutics we use can have profound effects on patient quality of life, and the decisions about treatment should reflect that reality.

If the assessment of our patient suggests aggressive treatment is appropriate, we first and foremost look for actionable mutations because they would likely yield the most benefit. If there are no targetable mutations/fusions (ie, EGFR, ALK, ROS, etc), then platinum doublets are still the cornerstone of front-line palliative chemotherapy. We routinely screen for, and offer, all pertinent trials to our patients.

Our preference is to use a platinum-based doublet in the front-line setting. The second agent in the doublet is usually a taxane or pemetrexed (based on the histology). We prefer pemetrexed in nonsquamous histology and paclitaxel in squamous histology. We believe that use of switch or continuation maintenance in the nonsquamous setting is quite beneficial.<sup>1,2</sup> Upon progression of the disease, we now favor nivolumab for second-line therapy. Beyond second line, if the patient is both functionally capable and psycho-

logically motivated to receive further treatment, then we will entertain erlotinib or a noncross-resistant, single-agent chemotherapy. Given the prognosis of advanced or metastatic NSCLC and limited effectiveness of current treatments in those cases, clinical trials are appropriate and encouraged in any line of therapy when available.

When it comes to using targeted therapies, we will often re-biopsy tumors to assess their genetic profile to see if second-line therapies would benefit the patient, especially in context of resistance mutations, and so on.

The scope of therapies for NSCLC is changing rapidly, and many new drugs are on the horizon. We are excited and hopeful that these therapies will begin to change the landscape of lung cancer treatment while providing meaningful benefit to our patients.

## References

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— Kartik Konduri, MD

whereas median duration of response was 8.4 months in the docetaxel arm but had yet to be reached in the nivolumab arm. PD-L1 levels were quantifiable in 83% of patients, but had neither prognostic nor predictive significance for any efficacy endpoint evaluated.

The safety of nivolumab was assessed by evaluating the incidence of adverse events (AEs). Treatment-related AEs, including both hematologic and nonhematologic malignancies, occurred less frequently with nivolumab than with docetaxel therapy. Serious AEs of any grade were observed in 7% and 24% of patients, respectively, and most frequently involved hypothyroidism, diarrhea, pneumonitis, increased blood creatinine levels, and rash. Grade 3/4 serious AEs occurred in 2% and 19% of patients, respectively, and in the nivolumab group common grade 3 events included tubulointerstitial nephritis, colitis, and pneumonitis. The median time to onset of treatment-related AEs in the nivolumab arm was 0.3-17.6 weeks. Treatment-related AEs led to discontinuation in 3% of nivolumab-treated patients, most commonly owing to pneumonitis, and 10% of docetaxel-treated patients, owing to peripheral neuropathy and fatigue. There were no deaths in the nivolumab arm, and 3 deaths in the docetaxel arm.

The prescribing information for nivolumab recommends

a dose of 3 mg/kg administered as an intravenous infusion over 1 hour every 2 weeks until disease progression or unacceptable toxicity. Warnings and precautions for the drug, which is marketed by Bristol-Myers Squibb as Opdivo, include immune-mediated pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, and hypo- and hyperthyroidism. It is recommended that patients be monitored for signs and symptoms of these toxicities throughout treatment, including for abnormal liver tests, elevated serum creatinine, and thyroid dysfunction.

No dosage adjustments are required in patients with renal impairment or with mild hepatic impairment, though nivolumab has not been studied in patients with moderate or severe hepatic impairment. Nivolumab should be withheld for grade 2 pneumonitis; grade 2/3 colitis; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3, and up to 5 times the upper limit of normal (ULN) or total bilirubin >1.5 up to 3 times the ULN; and other severe or grade 3 treatment-related AEs. Nivolumab administration can be resumed after appropriate treatment if AEs recover to grade 0/1. Treatment should be permanently discontinued after life-threatening grade 4 AEs, grade 3/4 pneumonitis, grade 4 colitis, AST/ALT >5 times the ULN or total bilirubin >3 times the ULN, creatinine

>6 times the ULN, severe or grade 3 treatment-related AEs that recur or are persistent, or grade 2/3 treatment-related AEs that don't resolve within 12 weeks of last dose.

#### References

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