



# 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.

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## 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%.<sup>1</sup> 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)<sup>2-6</sup> and anaplastic lymphoma kinase (ALK) inhibitors,<sup>7-9</sup> 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,<sup>10</sup> 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.<sup>11-13</sup>

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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.<sup>14,15</sup> 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.<sup>14</sup> The inhibitory receptors cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1<sup>16</sup> 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.”<sup>20</sup> 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.<sup>15,17-19</sup>

To date, several immune checkpoints inhibitors, including atezolizumab, durvalumab, nivolumab, and pembrolizumab, are under evaluation in different settings and histology subtypes of lung cancer.<sup>20-22</sup> Nivolumab binds PD-1 with high affinity and blocks its interactions with both B7-H1 and B7-DC.<sup>23</sup> 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.<sup>24</sup> 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.<sup>25</sup> 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%.<sup>26,27</sup>

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.<sup>28</sup>

### 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<sup>2</sup> 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.<sup>22</sup> 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

**Table 1** Check-Mate 017-Median Overall Survival and Overall Response Rate by PD-L1 Expression

PD-L1 Expression Level	Overall Survival			Overall Response Rate		
	Nivolumab N pts	Docetaxel N pts	Overall Survival Hazard Ratio (95% CI)	Nivolumab %	Docetaxel %	P Value
<1	54	52	HR = 0.58 (95% CI, 0.37-0.92)	17 (9/54)	10 (5/52)	.94
≥1	63	56	HR = 0.69 (95% CI, 0.45-1.05)	18 (11/63)	11 (6/56)	
<5	75	69	HR = 0.70 (95% CI, 0.47-1.02)	15 (11/75)	12 (8/69)	.29
≥5	42	39	HR = 0.53 (95% CI, 0.31-0.89)	21 (9/42)	8 (3/39)	
<10	36	33	HR = 0.70 (95% CI, 0.48-1.01)	16 (13/81)	11 (8/75)	.64
≥10	81	75	HR = 0.50 (95% CI, 0.28-0.89)	19 (7/36)	9 (3/33)	

Abbreviations: CI = Confidence interval; HR = hazard ratio; PD-L1 = programmed cell death ligand-1; pts = patients.

platinum-based doublet chemotherapy. For the twin trial conducted on squamous histology, patients were randomly assigned to receive nivolumab at a dose of 3 mg/kg every 2 weeks (292 patients) or docetaxel at a dose of 75 mg/mq every 3 weeks (290 patients) until disease progression. The primary endpoint was OS, and secondary objectives were investigator-assessed ORR, PFS, efficacy by PD-L1 expression, quality-of-life, and safety. The median OS was significantly higher for the nivolumab group: 12.2 months versus 9.4 months for the docetaxel group (HR 0.73, 95% confidence interval [CI], 0.59-0.89;  $P = .0015$ ). In addition, the 1-year OS was 51% for the nivolumab group compared with 39% for the docetaxel group. Survival benefits were seen for all subgroups of patients with the exception of patients who carried tumor *EGFR* mutations. The ORR was also significantly higher for patients receiving nivolumab compared with those receiving docetaxel (19% vs. 12%, respectively;  $P = .0246$ ). There were no significant differences in PFS. Seventy-eight percent (455/582) of randomized patients had quantifiable PD-L1 expression. Of the 292 patients that received nivolumab, PD-L1 expression ( $\geq 1\%$ ,  $\geq 5\%$ , and  $\geq 10\%$ ) was

identified in 123 (63%) patients that received nivolumab, while the remaining 108 (37%) patients had no PD-L1 expression.

For patients with tumor PD-L1 expression  $\geq 1\%$ ,  $\geq 5\%$ , and  $\geq 10\%$ , the results showed an increased median OS of 17.2 months, 18.2 months, and 19.4 months for patients treated with nivolumab compared with 9.0 months, 8.1 months, and 8.0 months for patients receiving docetaxel, respectively. The median OS for patients with tumors having less than 1%, less than 5%, and less than 10% of cells staining positive for PD-L1 was similar for nivolumab (range, 9.7-10.4 months) and docetaxel (range, 10.1-10.3 months; Table 2). AEs of any grade occurred in 69% of patients receiving nivolumab and 88% of patients receiving docetaxel, while grade 3-5 AEs occurred in 10% of patients in the nivolumab group and 54% of those in the docetaxel group.<sup>29</sup>

### Overview on the Safety Profile of Nivolumab

In both phase III trials of nivolumab as a second-line treatment of NSCLC patients with squamous and non-squamous histology, the agent was generally well-tolerated, with approximately 70% of

**Table 2** Check-Mate 057-Median Overall Survival and Overall Response Rate by PD-L1 Expression

PD-L1 Expression Level	Median Overall Survival, Months			Overall Response Rate		
	Nivolumab	Docetaxel	HR	Nivolumab	Docetaxel	P Value
<1	10.4	10.1	HR = 0.90 (95% CI, 0.66-1.24)	9	15	.0019
≥1	17.2	9.0	HR = 0.59 (95% CI, 0.43-0.82)	31	12	
<5	9.7	10.1	HR = 1.01 (95% CI, 0.77-1.34)	10	14	.0020
≥5	18.2	8.1	HR = 0.43 (95% CI, 0.30-0.63)	36	13	
<10	9.9	10.3	HR = 1.00 (95% CI, 0.76-1.31)	11	14	.0021
≥10	19.4	8.0	HR = 0.40 (95% CI, 0.26-0.59)	37	13	

Abbreviations: CI = Confidence interval; HR = hazard ratio; PD-L1 = programmed cell death ligand-1.

overall AEs, but only 10% grade 3 or 4 AEs. The most common adverse reactions ( $\geq 20\%$ ) reported with nivolumab were fatigue (about 20%) and decreased appetite (about 15%). Over the most frequent and well-known toxicities, a small group of patients developed a new kind of AE, which was considered to be an immune-related AE (irAE), as part of an immune-mediated response that was directed to different tissues. Overall, the incidence of irAEs was lower than 9% in both clinical trials (Check-Mate 017/057), and the most frequent irAEs were skin rash (9% all grades; 0% grade 3/4), hypothyroidism (4%-7% all grades; 0% grade 3/4), diarrhea and colitis (8% all grades; 0% grade 3/4), pneumonitis (3%-5% all grades; 0% grade 3/4), and increased hepatic function test (ALT/AST; 2%-3% all grades; 0% grade 3/4). These irAEs were well managed by administering systemic glucocorticoid. The median time to onset of treatment-related pulmonary events was 15.1 weeks (range, 2.6-85.1 weeks). In addition, all but 1 patient with pulmonary events received glucocorticoids, and all cases resolved, with a median time to resolution of 5.0 weeks (range, 0.6-12.1 weeks). Among the patients with resolved cases, 1 patient had a subsequent recurrence of pneumonitis, which was managed appropriately with glucocorticoid treatment. The median time to resolution of treatment-related select AEs ranged from 0.3 to 5.0 weeks in the nivolumab group.

These results confirm the high superiority of nivolumab compared with standard docetaxel alone, which presented an incidence of AEs with grade 3/4 in more than 50% of patients. However, careful monitoring of patients receiving nivolumab is required for better management of irAEs, and prompt and correct management with intravenous steroid therapy is needed.<sup>26-29</sup>

### Debating for Clinical Practice

#### *Can We Consider Nivolumab as a Standard Second-Line Option for Patients With Driver Mutations?*

In the Check-Mate-057 trial, only a small group of enrolled patients presented predictive biomarkers. In the nivolumab arm, 15% of patients were EGFR-positive and 4% presented ALK rearrangement, with comparable rates of 13% and 3%, respectively, in the docetaxel group. The subgroup of 82 patients with EGFR mutations who received nivolumab did not exhibit an improvement in OS (HR, 1.18; 95% CI, 0.69-2.00).<sup>30</sup>

Evidence suggests that patients with EGFR mutations may not achieve a response to immune checkpoint inhibitors due to different biologic or molecular changes that occur and drive tumor progression. Similarly, patients with no driver mutations have a better chance of responding because activated biologic pathways may intersect and thus activate a particular pathway or signal without the specific biomarker being activated or overexpressed.<sup>31</sup> Data regarding the correlation between PD-1/PD-L1 expression and EGFR mutations remain controversial. Preclinical research has shown that activation of EGFR signaling induces PD-L1 expression, which can aid lung tumors in escaping an antitumor immune response. Data from a phase I trial showed that NSCLC patients harboring an EGFR mutation did not achieve an objective response when treated with nivolumab.<sup>32</sup>

In a retrospective analysis of 125 patients with NSCLC, D'Incecco et al investigated the role and interactions between PD1/PD-L1 expression, EGFR or KRAS mutations, ALK translocations, and

EGFR/KRAS/ALK wild-type status. The authors observed that PD-1 positivity was significantly associated with the presence of KRAS mutations ( $P = .006$ ), while PD-L1 positivity was significantly associated with the presence of EGFR mutations ( $P = .001$ ). Patients with PD-L1 positivity had higher sensitivity to EGFR-TKIs as well as longer time-to-progression and OS ( $P = .09$ ) than PD-1-negative patients.<sup>15,33</sup>

### Recommendation

Although the available data are based on a small number of patients previously treated with EGFR TKIs or ALK inhibitors, at the present time, docetaxel plus nintedanib or docetaxel plus ramucirumab could be preferred to nivolumab as a second-line treatment for NSCLC patients with EGFR mutations T790M negative or T790M positive and treated with a third generation TKI or with ALK translocation. For patients with an EGFR mutation who progress after first-line therapy and develop a resistance driver mutation of T790, osimertinib or rociletinib should be considered as best treatment options. For patients with an ALK translocation, progressing to crizotinib in first- or second-line therapy, ceritinib, or alectinib should be considered in place of chemotherapy.

#### *Is PD-L1 Expression a Predictive Biomarker for the Selection of Non-Squamous Patients to Receive Nivolumab as a Second-Line Treatment?*

The results of the Check-Mate-057 trial confirmed the efficacy of nivolumab as a second-line treatment option for NSCLC patients and resulted in some interesting issues to be discussed. The first interesting point was the evaluation of PD-L1 expression as a potential predictive biomarker. In this trial, PD-L1 evaluation was performed as a retrospective analysis that considered archival biopsy samples rather than recent biopsy samples performed immediately prior to enrollment. In the Check-Mate-057 trial, 78% of randomized patients were analyzed for PD-L1 expression, and the rate of PD-L1-expressing tumors was balanced between 2 groups. Across the pre-specified 1%, 5%, and 10% expression levels, PD-L1 status was predictive of nivolumab benefit. These results confirmed that, in patients with PD-L1-positive tumors, there was a striking OS benefit after treatment with nivolumab, while in patients with no PD-L1 expression, no statistical difference was noted between nivolumab and docetaxel (Table 1).

These data open a big debate regarding the utilization of PD-L1 expression as a biomarker for patient selection. Indeed, the evaluation of PD-L1 expression by immunohistochemistry (IHC) is currently confounded by multiple unresolved issues, including variable detection antibodies, differing IHC cutoffs, tissue preparation, processing variability, primary versus metastatic biopsies, oncogenic versus induced PD-L1 expression, and staining of tumor versus immune cells. Emerging data suggest that patients whose tumors overexpress PD-L1 by IHC have improved clinical outcomes with anti-PD-1-directed therapy, but the presence of robust responses in some patients with low levels of expression of these markers complicate the use of PD-L1 expression as an exclusive predictive biomarker.<sup>28</sup> Furthermore, in the Check-Mate 017 study, PD-L1 expression was not predictive of outcome in patients with squamous histology.



Data from clinical trials assessing the treatment of NSCLC patients with different immune checkpoint inhibitors have shown that patients with PD-L1 expression tend to have more robust responses to anti-PD-L1 therapy. It is very interesting to note that there is a subset of patients that do not express PD-L1 who still achieve a benefit in survival and response rate (range from 0% to 15%) when treated with nivolumab.

### Recommendation

At the present time, it is not possible to consider PD-L1 as a definitive biomarker for the selection of non-squamous patients in the second-line setting. However, based on available data, nivolumab should be considered as a new standard-of-care for second-line treatment of patients with NSCLC progressing after platinum-based first-line treatment and who are wild-type for EGFR and ALK.

In patients with squamous NSCLC, considering the results of the Check-Mate-017 trial showing nivolumab activity independent of PD-L1 expression, nivolumab should be considered as the gold standard of treatment in the second-line setting. However, the evaluation of PD-L1 expression is mandatory for consideration of pembrolizumab, which is only approved in the US as a second-line treatment in patients with high PD-L1.

## New Options for Second-Line Nintedanib

Nintedanib is an oral angiokinase inhibitor that targets VEGFR 1-3, FGFR 1-3, and PDGFR  $\alpha$  and  $\beta$ , which was evaluated in combination with docetaxel as second-line treatment for patients with NSCLC in a randomized, double-blind, phase III trial (LUME-Lung 1). In this study, 1341 patients were randomized to receive nintedanib 200 mg twice daily plus docetaxel 75 mg/m<sup>2</sup> once a day for 3 weeks ( $n = 655$ ) or placebo plus docetaxel ( $n = 659$ ). The results showed that nintedanib plus docetaxel improved PFS in the intent-to-treat population compared with docetaxel plus placebo (3.4 vs. 2.7 months, respectively; HR, 0.79; 95% CI, 0.68-0.92;  $P = .0019$ ). In a subgroup of patients with adenocarcinoma histology, the median OS was 12.6 months versus 10.3 months, respectively (HR, 0.83; 95% CI, 0.70-0.99;  $P = .0359$ ), in favor of patients treated with the combination. The safety profile of patients treated with nintedanib showed a low incidence of class effects typically associated with antiangiogenic agents. Based on these results, nintedanib was approved by European Medicine Agency (EMA) for second-line therapy in the adenocarcinoma setting.<sup>34</sup>

## Ramucirumab

Ramucirumab, a human IgG1 monoclonal antibody targeting VEGFR-2, was evaluated in combination with docetaxel in the REVEL trial, which overlapped with the same setting of the LUME-Lung 1 trial. In this study, 1253 patients were randomized (1:1) to receive docetaxel 75 mg/m<sup>2</sup> and either ramucirumab (10 mg/kg) or placebo on day 1 of a 21-day cycle until disease progression. The results showed increased OS for patients receiving docetaxel plus ramucirumab (10.5 vs. 9.1 months, respectively; HR, 0.86; 95% CI, 0.75-0.98;  $P = .023$ ). Progression-free survival was also significantly longer for patients receiving ramucirumab plus docetaxel (HR, 0.76; 95% CI, 0.68-0.86;  $P < .001$ ). Considering these results, the US Food and Drug Administration (FDA) approved

ramucirumab in combination with docetaxel to treat patients with NSCLC who progress after a first-line therapy.<sup>35</sup>

## Pembrolizumab

Pembrolizumab is an immune checkpoint inhibitor against PD-1 that received accelerated approval by the FDA for the treatment of NSCLC with expression of PD-L1 after first-line platinum therapy based on data from the KEYNOTE-001 trial. This trial evaluated the efficacy of pembrolizumab in 550 patients with NSCLC who exhibited PD-L1 expression on at least 50% of tumor cells. More recently, a randomized phase III trial (KEYNOTE-010) evaluated the role of pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks versus docetaxel in 1034 patients with PD-L1 positive (PD-L1 expression on at least 50% of tumor cells) NSCLC progressing after platinum-based chemotherapy. Overall survival was significantly longer for patients treated with pembrolizumab 2 mg/kg than with docetaxel (median OS, 14.9 vs. 8.2 months, respectively; HR, 0.54; 95% CI, 0.38-0.77;  $P = .0002$ ) and with pembrolizumab 10 mg/kg than with docetaxel (median OS, 17.3 vs. 8.2 months, respectively; HR, 0.50; 95% CI, 0.36-0.70;  $P < .0001$ ). These interesting results confirm the high efficacy of pembrolizumab for NSCLC patients with PD-L1 expression in the second-line setting.<sup>36</sup>

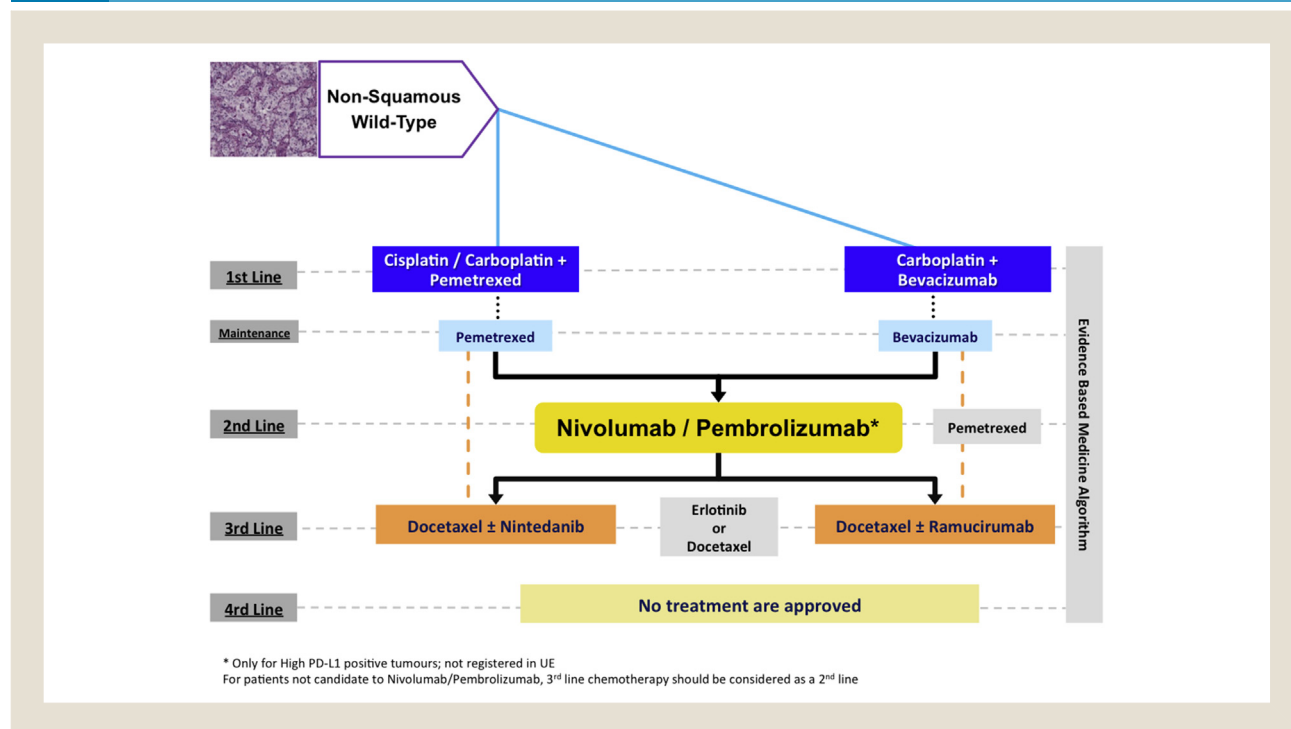
## Reasoned Discussion

### Algorithm and Considerations for Second-Line Treatment of Non-Squamous NSCLC

For patients with adenocarcinoma/non-squamous NSCLC who are wild-type for driver mutations, the previous treatment scenario only suggested 3 approved drugs for the second-line setting: docetaxel, pemetrexed, and erlotinib. However, these agents never fully satisfied oncologists' expectations in terms of survival benefit and safety profile. Docetaxel, which has been considered a cornerstone of second-line treatment options for over 20 years, was consistently burdened by a safety profile with high incidence of grade 3/4 AEs. The combination of docetaxel  $\pm$  the addition of new anti-angiogenic agents (nintedanib or ramucirumab) can be considered 1 step forward in terms of progress but remains a less than satisfactory treatment option.

In this view, the results of the Check-Mate 057 phase III trial confirmed that the chemotherapy era in the second-line setting is coming to the end. As discussed above, there are currently no limitations for considering nivolumab as a new standard-of-care in the second-line setting for non-squamous patients as well. It is clear that there is a group of patients that receive a great benefit from treatment with nivolumab compared with others, but at the present time, it is not possible to consider PD-L1 expression as a definitive predictive biomarker for patient selection. For patients that progress to nivolumab in second-line, the combination of docetaxel plus the anti-VEGFR agent nintedanib or ramucirumab could be evaluated for selected patients (usual selection criteria for antiangiogenic treatment in terms of tumor characteristics and patient comorbidities). Pemetrexed remains a good option for patients that did not receive this agent in the first-line setting and single agent docetaxel as an alternative. In addition to these chemotherapy agents, the use of erlotinib should be considered for patients who are not candidates for chemotherapy (Figure 1).

**Figure 1** Algorithm for Treatment of Non-Squamous NSCLC



Abbreviations: NSCLC = Non-small-cell lung cancer; PD-L1 = programmed cell death ligand-1.

## Algorithm and Considerations for Second-Line Treatment of Squamous NSCLC

The results of the Check-Mate 017 study markedly changed our consideration regarding second-line treatment of squamous NSCLC. The strong and homogenous data confirmed the high efficacy of nivolumab as a second-line treatment in patients that progressed after a first-line treatment with platinum-based chemotherapy. The significant difference in survival moved nivolumab into consideration as a new standard treatment. For patients that present limitations in receiving nivolumab, docetaxel plus ramucirumab can be considered as valid alternatives in selected patients (usual selection criteria for anti-angiogenic treatment based on characteristics of tumor and patients comorbidities), though this treatment combination is not yet approved worldwide. In patients who are unsuitable for ramucirumab, single agent docetaxel should be considered. In patients who progress to nivolumab and docetaxel-based therapy, erlotinib or afatinib could be eventually considered in subsequent lines (Figure 2).

## Conclusion

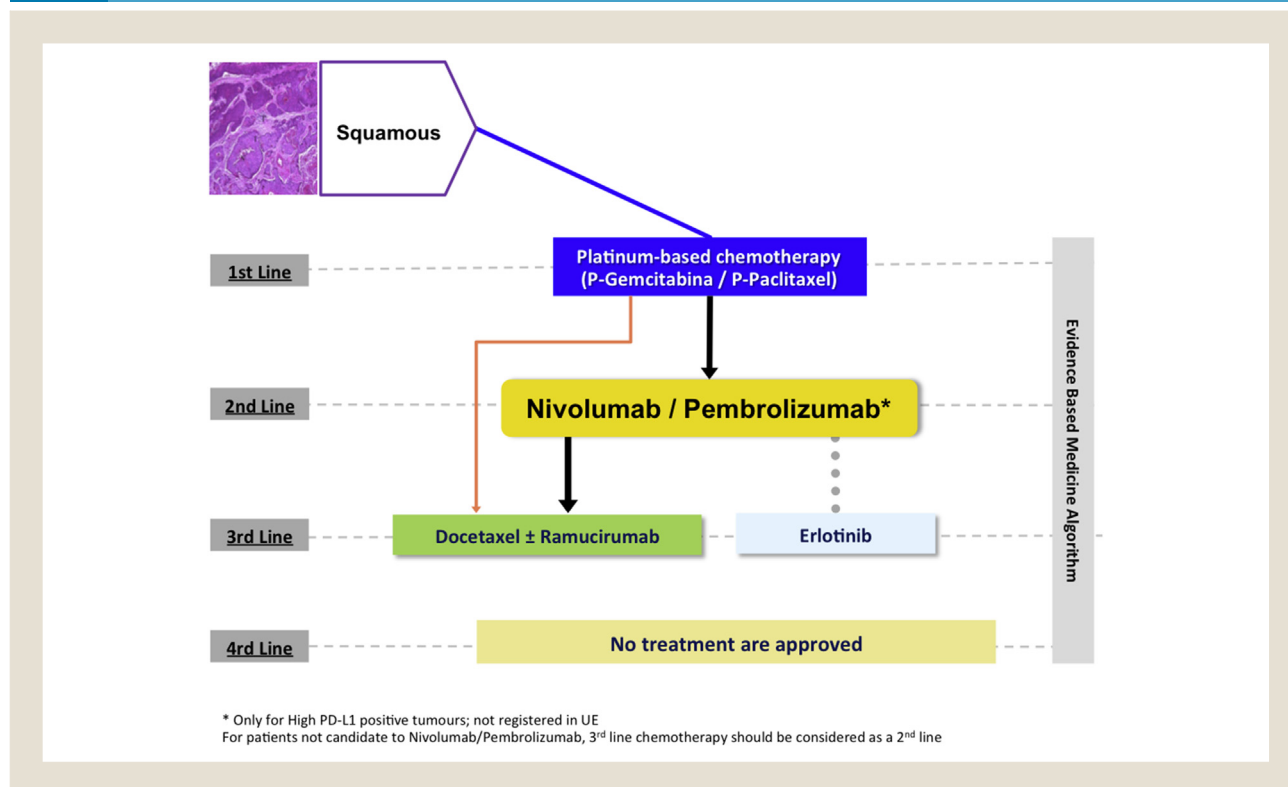
In recent years, we have witnessed great changes in the treatment of NSCLC patients with driver mutations, but too few options have been available for patients with wild-type non-squamous or squamous subtypes. The use of a platinum combination with pemetrexed or bevacizumab as a first-line therapy has shown an improvement in the overall survival of non-squamous patients. However, for approximately 60% of patients progressing to the first-line therapy, limited therapeutic options were available until more recently. The development of new targeted agents for the treatment

of NSCLC with driver mutations, and in particular EGFR and ALK, has changed our clinical treatment approach for approximately 15% of patients. Unfortunately, for the remaining 85% of patients, chemotherapy remains the only available and effective treatment.

The initial data regarding immune checkpoint inhibitors were promising and a multitude of clinical trials have followed in the past few years. Nivolumab was the first immunotherapy agent used for the treatment of NSCLC that was shown to be superior in terms of efficacy and safety compared with standard second-line chemotherapy (docetaxel). Twin randomized phase III trials also evaluated the efficacy and safety of nivolumab in squamous and non-squamous populations as a second-line treatment. These results suggest that in patients with advanced squamous NSCLC, nivolumab should be considered as the new gold standard-of-care in the second-line setting. The drug has been approved with this indication in the US by the FDA and in Europe by the EMA.

For patients affected by non-squamous NSCLC who progress to a first-line treatment, nivolumab should be considered as a standard-of-care as well with the exception of patients who harbor EGFR mutations or an ALK translocation, as pervious discussed. To date, PD-L1 expression cannot be considered as a predictive biomarker to use in clinical practice for the selection of patients for nivolumab treatment. Further investigation on the predictive power of PD-L1 expression is ongoing with other PD-1 and PD-L1 inhibitors. In addition to the approval of nivolumab, the FDA has granted pembrolizumab accelerated approval status as a second-line therapy for patients with NSCLC who exhibit high

Figure 2 Algorithm for Treatment of Squamous NSCLC



Abbreviations: NSCLC = Non-small-cell lung cancer; PD-L1 = programmed cell death ligand-1.

PD-L1 expression based on assessment with the companion diagnostic PD-L1 IHC 22C3 pharmDx test.

## Disclosure

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