Biomarkers for the response to immunotherapy in patients with non-small cell lung cancer

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1 New targeted treatments for non-small cell lung cancer – role of nivolumab

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Abstract

Non-small-cell lung cancer (NSCLC) is often diagnosed at an advanced stage of disease, where it is no longer amenable to curative treatment. During the last decades, the survival has only improved significantly for lung cancer patients who have tumors harboring a driver mutation. Therefore, there is a clear unmet need for effective therapies for patients with no mutation. Immunotherapy has emerged as an effective treatment for different cancer types. Nivolumab, a monoclonal inhibitory antibody against PD-1 receptor, can prolong survival of NSCLC patients, with a manageable toxicity profile. In two Phase III trials, nivolumab was compared to docetaxel in patients with, respectively, squamous (CheckMate 017) and non-squamous NSCLC (CheckMate 057). In both trials, nivolumab significantly reduced the risk of death compared to docetaxel (41% and 27% lower risk of death for squamous and non-squamous NSCLC, respectively). Therefore, nivolumab has been approved in the US and in Europe as second-line treatment for advanced NSCLC. Unfortunately, accurate predictive factors for patient selection are lacking, making it difficult to decide who will benefit and who will not. Currently, many ongoing trials evaluate the efficacy of nivolumab in different settings and in combination with other agents. This paper reviews the present literature about the role of nivolumab in the treatment of NSCLC. Particular attention has been given to efficacy studies, toxicity profile, and current and emerging predictive factors.

Keywords: advanced non-small-cell lung cancer; anti-PD-1; immunotherapy; nivolumab.

Introduction

Lung cancer is the leading cause of cancer death worldwide, with 1.825 million diagnoses and 1.59 million deaths in 2012 [66] and is the most commonly diagnosed malignancy in males. The major cause of lung cancer is smoking, which is responsible for 80% of cases in males and 50% of cases in females [12]. Non-small-cell lung cancer (NSCLC) accounts for ~85%–90% of all lung cancers. The two major subtypes are non-squamous cell (mainly adenocarcinoma) and squamous cell carcinomas [14, 67]. In the majority of cases, patients are diagnosed at an advanced, unresectable stage of disease. For these patients, the treatment has a palliative intent, aiming to control symptoms and prolong survival.

In the last decades, the discovery of genomic heterogeneity of NSCLCs has radically changed the diagnostic approach for these patients. With the advent of new techniques (integrating morphological analysis, immunohistochemistry, and molecular testing), different subclasses of NSCLCs have been defined (Figure 1) [68]. Targetable alterations are the key elements for personalized treatments and are nowadays part of the standard of care for NSCLC patients. However, a targetable driver mutation is detectable only in 10%–20% of all NSCLCs in the Caucasian population (Table 1) [17, 67, 68]. For the others, chemotherapy has been the only available option so far, with dismal results.

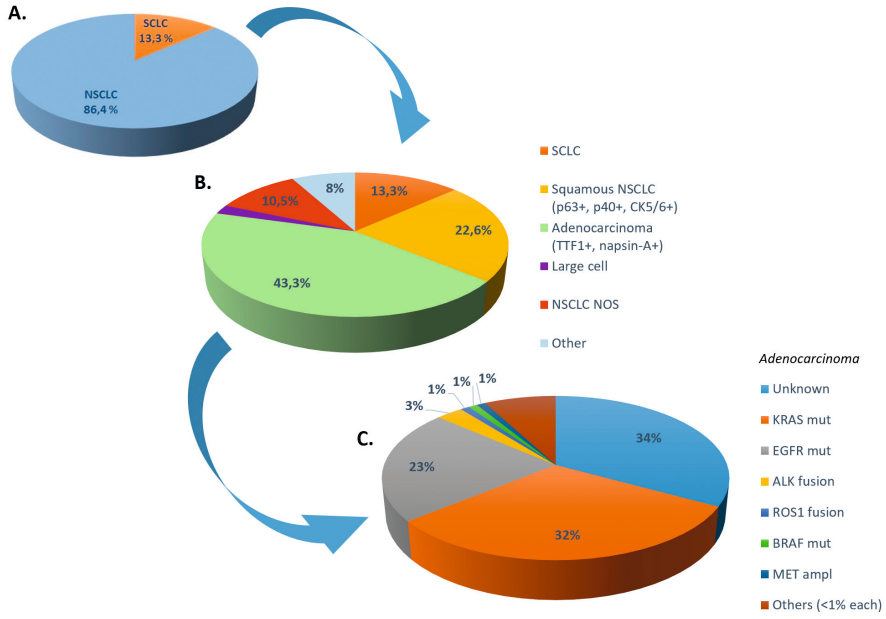

Figure 1 - Multistep process for the diagnosis and characterization of lung cancer.
Notes: *(A) The two main lung cancer subtypes, SCLC and NSCLC, can be discriminated by a morphological analysis. NSCLC accounts for ~85%–90% of all lung cancers. (B) Immunohistochemistry allows different NSCLC subtypes to be distinguished. (C) Molecular testing allows possible driver mutations in the tumor to be identified (EGFR and ALK). Analysis of ROS1, BRAF, and MET should be considered for selected patients. Data from National Cancer Institute [73] and Naidoo et al [5].*
Abbreviations: *SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer; NOS, non-squamous.*

In the last years, new agents have been developed which enhance the host immune response against the tumor. Immune checkpoint inhibitors have been shown to be highly active in different malignancies [18]. The anti-PD-1 monoclonal antibody (mAb) nivolumab has recently been shown to induce a significant survival benefit in NSCLC patients, with either squamous or non-squamous histology, compared to standard second-line chemotherapy [3, 5] thus providing a new treatment option in this setting.

The aim of this paper is to present the standard of treatment and review the clinical data about the role of nivolumab in the treatment of NSCLC, in terms of efficacy, safety, and patients' quality of life (QoL) [69-71].

Current and emerging treatment options for NSCLC

Until recently, chemotherapy has been the only available option for patients diagnosed with NSCLC not amenable to radical-intent local treatment. First-line chemotherapy doublet regimens, based on platinum compounds (cisplatin or carboplatin) combined with a third-generation agent (vinorelbine, gemcitabine, paclitaxel, docetaxel, pemetrexed), prolong survival and improve QoL. Mono-chemotherapy is considered the treatment of choice both as second line and for unfit or elderly patients [14]. In the last decade, with the discovery of driver mutations in a variable percentage of NSCLCs (mainly in never smokers or light former smokers, with a non-squamous histology), targeted therapies have emerged as new standard of care in this setting (Table 1). For tumors with an activating mutation, in the HER domain, EGFR-tyrosine kinase inhibitors, gefitinib, erlotinib, and afatinib, have shown higher efficacy, in terms of response rate (RR) and progression-free survival (PFS), compared to chemotherapy [72-75]. Similar results have been achieved by the ALK-tyrosine kinase inhibitors crizotinib and ceritinib, in tumors with ALK rearrangement [76-78]. More recently, new primary or acquired targetable molecular alterations have been identified, such as ROS1 rearrangement, MET amplification, and HER2 mutation. A number of Phase I and II trials have shown encouraging results (Table 1) [78-87], so molecular testing is now recommended for these genes in selected patients.

Recently, new immune-modulating drugs have been developed which target different immune checkpoints, with the aim of enhancing the host immune response against tumor cells. For patients with NSCLC, the best results have been shown by PD-1/PD-L1 immune checkpoint inhibitors, which might have a higher activity in high-mutational load tumors [88]. Nivolumab (Opdivo®; Bristol-Myers Squibb, New York, NY, USA; other names: BMS-936558, MDX-1106, ONO-4538), a PD-1-blocking antibody, has been approved by the US Food and Drug Administration (FDA) as second-line treatment for squamous NSCLC in March 2015. In October 2015, the FDA expanded its approved use to all NSCLCs (both squamous and non-squamous histology) that have progressed after a first-line platinum-based chemotherapy [3, 5].

Table 1 - Driver mutations, and current and emerging targeted treatments in NSCLC.

Molecular alteration	Frequency	Targeted agent	Studies and findings
EGFR mut (exon 19-21)	*Caucasian pts*: 10-15% NSCLCs *Asian pts*: 50% NSCLCs (Common mut: *Ex 19 Del*: 45%; *Ex 21 L858R*: 40%)	***Gefitinib*** ***Erlotinib*** ***Afatinib***	IPASS [72]: 1st line Gefitinib is superior to Carbo-Paclitaxel in terms of RR (71% *vs* 47%) and PFS (9.5m *vs* 6.3m) in Asian, non-smoker pts, with ADC NEJSG002 [89]: 1st line Gefitinib is superior to Carbo-Paclitaxel in terms of RR (73% *vs* 30%) and PFS (10.8m *vs* 5.4m) in EGFR+ ADC EURTAC [73]: 1st line Erlotinib is superior to platinum-based ChT for RR (55% *vs* 11%) and PFS (9.7m *vs* 5.2m) in Caucasian pts with EGFR+ ADC LUX-Lung 3[80]: 1st line Afatinib is superior to Cis-Pem for RR (56% *vs* 23%) and PFS (11m *vs* 6.9m) in EGFR+ ADC LUX-Lung 6 [75]: 1st line Afatinib is superior to Cis-Gem for RR (67% *vs* 23%) and PFS (11m *vs* 5.6m) in EGFR+ ADC Pooled analysis LUX-Lung 3/6 [90]: 1st line Afatinib improves OS (31.7m *vs* 20.7m) for EGFR ex19del ADC compared to platinum-based ChT
EGFR mut (ex 20 T790M)	*Acquired resistance to 1st line EGFR TKi*: 50% pts	***AZD9291*** ***CO-1686*** ***(Rociletinib)***	AZD9291 phase I[79] : AZD9291 is effective in pts with T790M+ and T790M neg ADC, after a previous TKi treatment, with DCR=84% (*T790M+*: 95%; *T790M neg*: 61%) and median PFS=8.2m (*T790M+*: 9.6m; *T790M neg*: 2.8m) CO-1686 phase I/II [80]: Rociletinib achieves high DCR in pretreated, caucasian, T790M+ (93%) and T790M neg (59%) ADC pts, with median PFS 13.1m for T790M+ pts (80% pts censored)
ALK translocation	2-7% NSCLCs	***Crizotinib*** ***Ceritinib*** ***Alectinib***	PROFILE 1007 [76]: Crizotinib is superior to Pem *or* Docetaxel as 2nd line therapy in ALK+ NSCLC, in terms of RR (65% *vs* 20%) and PFS (7.7m *vs* 3m) PROFILE 1014 [77]: Crizotinib is superior to platinum-Pem as 1st line therapy in ALK+ NSCLC, in terms of RR (74% *vs* 45%) and PFS (10.9m *vs* 7m) ASCEND-1 phase I[78]: Ceritinib is effective for ALK+ NSCLCs, both pre-treated with or naïve to Crizotinib (RR=58%; PFS=7m) AF-001JP phase I/II [81]: Alectinib is effective for the treatment of ALK+ Crizotinib naïve pts (RR=93.5%; PFS=27.7m) AF-002JG phase I/II [82]: Alectinib is effective for the treatment of ALK+ Crizotinib-resistant pts (RR=55%; PFS N/R)
ROS1 rearrangement	1-2% NSCLCs	***Crizotinib***	Phase I [83]: Crizotinib achieves 72% ORR in pts with ROS1 rearranged NSCLC; estimated median duration of response: 17.6 m; median PFS: 19.2 m
MET amplification	<1% ADC	***Crizotinib***	Ongoing phase I trial NCT00585195 (PROFILE 1001)[84]: 13 pts (low/intermediate/high level of amplification) 4 PR (mainly highly amplified NSCLCs); 6 ongoing at data-cutoff Diarrhea (50%), nausea and vomiting (31%), peripheral edema (25%)

Table 1 - Driver mutations, and current and emerging targeted treatments in NSCLC. *(Continued)*

Molecular alteration	Frequency	Targeted agent	Studies and findings
BRAF V600E mutation	<2% NSCLCs	***Dabrafenib*** ***Dabrafenib + Trametinib*** *(MEK-inhib.)*	Ongoing phase II trial NCT01336634[85]: 84 pts in total (78 pretreated; 6 treatment naïve) Pretreated pts (n=78): 25 PR (ORR: 32%); DCR>12weeks: 56%; median duration of response: 11.8 months (95% CI, 5.4-N/R) Naïve pts (n=6): 3 PR (4 pts evaluable for response) Ongoing phase II trial NCT01336634[86]: 33 pts (24 pts evaluable for response) Response (n=24): 15 PR (ORR 63%); DCR>12weeks: 88% Common AEs (>20%): pyrexia, diarrhea, nausea, vomiting, peripheral edema, rash. Grade 3-4 AEs: 39% pts
HER2 mutation	3% ADC (2% NSCLCs)	***Trastuzumab*** *or* ***Afatinib***	Retrospective [87]: 65 pts HER2 ex 20 mut; 33 pts received HER2-targeted therapy ORR=56%; overall DCR: 82% (*Trastuzumab*: 96%; *Afatinib*: 100%) PFS for HER2-targeted therapies: 5.1 months
RET rearrangement	1-2% ADC	***Cabozantinib***	Ongoing phase II trial NCT01639508 [91] *:* 5 pts: 3 evaluable for response to treatment with Cabozantinib Early and durable response

Note: *EGFR+ represents EGFR mutation positive (ie, activating mutations)*
Abbreviations: NSCLC, non-small-cell lung cancer; pts, patients; RR, response rate; PFS, progression-free survival; ADC, adenocarcinoma; ChT, chemotherapy; Cis, cisplatin; Pem, pemetrexed; OS, overall survival; TKI, tyrosine kinase inhibitor; DCR, disease control rate; N/R, not reported; ORR, overall response rate; PR, partial response; CI, confidence interval; AEs, adverse events.

Pharmacology of nivolumab

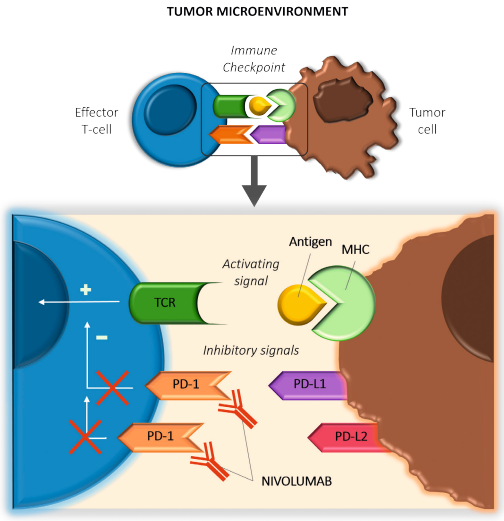

Figure 2 - Immuno-modulatory role of PD-1 receptor and mechanism of action of nivolumab.
Abbreviations: MHC, major histocompatibility complex; TCR, T-Cell Receptor; PD-1, programmed death 1; PD-L1, programmed death 1 – ligand 1; PD-L2, programmed death 1 – ligand 2.

Mechanism of action and pharmacodynamics

Nivolumab is a fully human IgG4 immune checkpoint inhibitory antibody, which binds to PD-1, preventing its interaction with its ligands PD-L1 (also called B7-H1 or CD274) and PD-L2 (also called B7-DC or CD273) (**Figure 2**) [92, 93]. PD-1 is an immune-regulatory receptor expressed by activated T-cells, and it is induced during any inflammatory reaction. PD-1 is also highly expressed by $CD4^+$ regulatory T (Treg) cells, and its main role is to limit immune response and maintain immune tolerance within peripheral tissues [94, 95], by both limiting the activity of effector T-cells and enhancing activity of inhibitory Treg cells [92]. Therefore, the interaction of nivolumab with PD-1 attenuates the negative signals of PD-1/PD-L1, thus enhancing the host antitumor immune response. Tumor infiltrating lymphocytes have been found to express PD-1 in different cancer types, while the upregulation of PD-L1 by tumor cells has been interpreted as a possible mechanism of resistance of the tumor to the host immune response [92, 96]. Lastly, PD-1-deficient mice showed a mild, late-onset immunological phenotype compared to the CTLA4-deficient ones, suggesting a more tolerable toxicity profile. These observations, taken all together, provided the basis for starting the development of new PD-1-targeted immunomodulatory compounds [18]. Preclinical studies have demonstrated that antibody-mediated PD-1/PD-L1 pathway blockade leads to an increase in T-cell count (both effector and antigen-specific) and modulates cytokines secretion in vitro and in murine models [97, 98]. The inhibition of PD-1 interaction with its ligand PD-L1, by specific mAbs, was able to rescue cytolytic immune antitumor activity, leading to tumor regression in mice [96].

The interaction of nivolumab with PD-1 receptor was evaluated using purified human T-cells from peripheral blood [10]. Nivolumab binds with high affinity to PD-1 on effector and memory T-cells and on Treg cells [10], thus preventing its interaction with PD-L1 and PD-L2. Neither $CD4^{+-}$ nor $CD8^{+-}$naïve T-cells are bound by nivolumab [10], reflecting the pattern of expression of PD-1, which is upregulated in activated T-cells in peripheral tissues [92]. Preclinical data showed that nivolumab binds to PD-1 on activated human $CD4^+$ T-cells with a half-maximal effective concentration (EC_{50}) of 0.64 nmol/L and inhibits PD-1 interaction with its ligands (PD-L1 and PD-L2) with a half-maximal inhibitory concentration (IC_{50}) of 2.52 and 2.59 nmol/L, respectively[10]. The high affinity of nivolumab for PD-1 has been confirmed in the first-in-human Phase I study by the analysis of PD-1 occupancy on circulating T-cells, which was demonstrated to be dose independent. Mean peak occupancy was 85% (range: 70%–97%), and the mean plateau occupancy was 72% (range: 59%–81%), detected after 4 hours to >57 days after the first infusion [1]. Plateau occupancy was maintained even when serum levels were undetectable [1]. Repeated infusions of nivolumab 10 mg/kg led to troughs and peaks of PD-1 occupancy around each dose, but 100% occupancy was not achieved [1].

Pharmacokinetics

Nivolumab is administered by intravenous infusion within 30–60 minutes. Pharmacokinetic data from the first-in-human Phase I trial demonstrated a half-life ranging between 12 (for subjects receiving the lowest doses: 0.3, 1, or 3 mg/kg) and 20 days (for subjects receiving the highest dose of 10 mg/kg), with a maximum serum

concentration directly related to administered dose within 4 hours after administration [1, 7]. No maximum dose has been defined [1, 7].

Nivolumab and NSCLC

Efficacy studies

Preclinical studies showed that nivolumab/PD-1 interaction leads to enhanced T-cell reactivity in vitro, in the presence of an antigen or another T-cell receptor stimulus [10]. Moreover, mAb inhibition of PD-1/PD-L1 interaction was able to rescue a cytolytic immune antitumor activity and lead to tumor regression in mice [96].

A Phase I trial with expansion cohorts was conducted between 2008 and 2012 (Figure 3 and Table 2), aiming to assess activity and safety of biweekly nivolumab at a dose of 1–10 mg/kg. A total of 296 heavily pretreated patients with advanced tumor were enrolled, including melanoma, NSCLC, renal cell carcinoma, and prostate and colorectal cancer. About one in four to one in five patients experienced durable objective response (OR), in particular those with melanoma, NSCLC, and renal cell cancer [7]. Given the encouraging results observed for NSCLCs, both in terms of RR and duration of response (DOR), an efficacy analysis based on data from a prolonged follow-up was carried out for this group of patients. In total, 129 patients with NSCLC underwent a median follow-up of 39 months (range: 32–66 months) and were evaluated for overall survival (OS), RR, and DOR [9]. Overall, median OS was 9.9 months (95% confidence interval [CI] 7.8–12.4), with a 1-, 2-, and 3-year survival rate of 42%, 24%, and 18%, respectively, without significant differences between squamous and non-squamous histologies. OS was longer for patients receiving nivolumab at the dose of 3 mg/kg (median OS =14.9 months, 95% CI 7.3–30.3), which was the dose of choice for the subsequent Phase III trials. Across all doses, overall response rate (ORR) was 17%, for both histological subtypes, but was higher for patients receiving 3 or 10 mg/kg doses compared to 1 mg/kg. Median estimated DOR for responders was 17 months, and an additional 10% of patientsexperienced long-lasting stability of disease (ie, stable disease [SD] ≥24 weeks) [9].

Given these encouraging results, a Phase II trial (CheckMate 063) was conducted between 2012 and 2013 (Figure 3 and Table 2) to investigate the efficacy of biweekly nivolumab 3 mg/kg, in patients with advanced squamous NSCLCs that had progressed after at least one platinum-based chemotherapy regimen and one more subsequent line of treatment. The efficacy of nivolumab was confirmed in this highly refractory group of patients, with 14.5% subjects achieving a partial response (PR) and 26% SD, with a high proportion of patients experiencing a durable response, in both groups [2]. Updated survival data were presented during the 2015 World Conference on Lung Cancer (WCLC) [37]. Out of 17 patients who achieved a PR, 13 (76%) had ongoing responses; thus, median DOR was not reached. Overall, median OS was 8.2 months (95% CI 6.1–10.9), and 1-year OS rate was 41%. Two Phase II Japanese trials achieved similar results in terms of ORR. Nivolumab-treated squamous NSCLC (n=35) showed an ORR of 25.7% (95% CI 14.2–42.1), while the ORR of non-squamous NSCLC (n=76) was 19.7% (95% CI 12.3–30.0) [99].

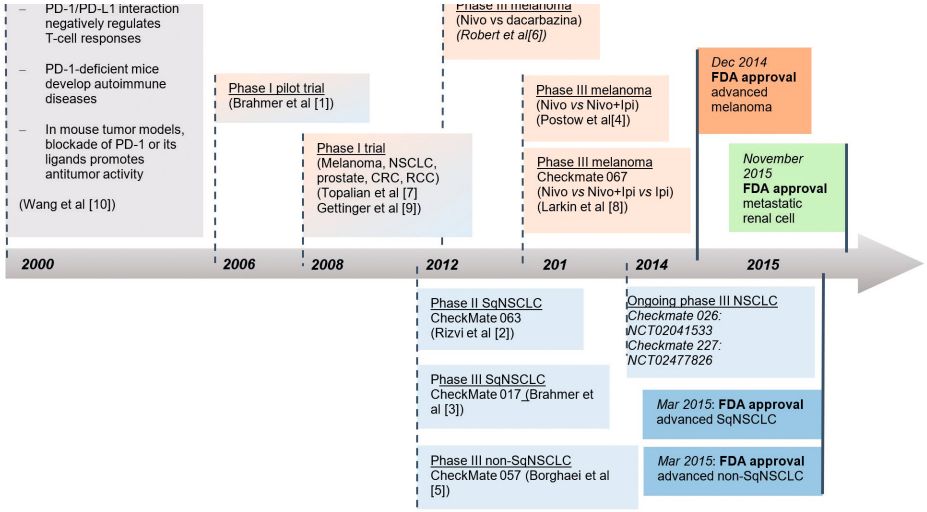

Figure 3 - Nivolumab development, from preclinical experience to clinical approval: focus on NSCLC.

Notes: *Timeline of nivolumab development from the preclinical studies to US FDA approval (dotted lines represent the starting date of the related trial).*

Abbreviations: PD-1, programmed death 1; PD-L1, programmed death 1 – ligand 1; *NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; RCC, renal cell carcinoma; Nivo, nivolumab; Ipi, ipilimumab; FDA, US Food and Drug Administration; SqNSCLC, squamous NSCLC.*

The results achieved in the Phase II trial were confirmed by the two subsequent Phase III trials of second-line treatment nivolumab (**Figure 3**). CheckMate 017 and CheckMate 057 aimed to compare second-line treatment nivolumab (given biweekly at the dose of 3 mg/kg) to standard-of-care docetaxel monotherapy (75 mg/m^2, every 3 weeks), in advanced squamous (272 patients) and non-squamous (582 patients) NSCLC patients, respectively[8, 9]. In both trials, nivolumab significantly reduced the risk of death compared to docetaxel (41% and 27% lower risk of death for squamous and non-squamous histologies, respectively). For patients with squamous NSCLC, median OS was 9.2 months (95% CI 7.3–13.3) in the nivolumab group and 6 months (95% CI 5.1–7.3) in the control group, while for non-squamous NSCLC, OS was 12.2 months (95% CI 9.7–15.0) with nivolumab and 9.4 months (95% CI 8.1–10.7) with docetaxel. At 18 months of analysis, the OS rate was 28% vs 13% for squamous and 39% vs 23% for non-squamous carcinoma. Moreover, subgroup analysis from CheckMate 057 identified a lack of survival benefit with nivolumab in never smokers and EGFR-mutated tumors, albeit a small patient population [5]. This is in line with the Phase I trial, where nivolumab achieved a higher RR among current and former smokers compared to never smokers [9]. Both observations may find an explanation in the higher mutational load of smoking-induced tumors, which can lead to the production of a higher number of tumor-associated neo-antigens [100].

The results of previous trials have been recently confirmed in a large (n=824) ongoing study (CheckMate 153) conducted in community-based oncology centers. Among patients with advanced pretreated NSCLC, until now, no differences have been reported in terms of safety [101]. Among the 395 patients evaluable for tumor response, 55 (14%)

experienced a PR, and 194 (49%), a SD. No differences have been observed according to PD-L1 status or baseline performance status[101].

A number of trials are currently ongoing (**Table 2** and **Figure 3**) evaluating the role of nivolumab (alone or in combination) as first-line treatment for advanced NSCLC. Preliminary results from the Phase I trial CheckMate 012 (ClinicalTrials.gov: NCT01454102) have been presented during the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting. In the cohort of the 52 chemotherapy-naïve patients who received nivolumab monotherapy, an ORR of 21%, with long DOR (median DOR not reached; range: 7.6+, 85.6+ weeks), was reported [36]. A Phase III trial (CheckMate 026, ClinicalTrials.gov: NCT02041533), comparing the first-line nivolumab to investigator's choice chemotherapy, in PD-L1-positive NSCLC, is currently ongoing [102].

During the 2015 WCLC, a manageable toxicity profile of nivolumab in combination with the CTLA4 immune checkpoint inhibitor ipilimumab (Yervoy™; Bristol-Myers Squibb; other names: MDX-010, MDX-101), in patients with NSCLC was reported. The ORR was 13%–39% across the four cohorts treated with different nivolumab and ipilimumab doses, but higher partial RRs were seen among patients who received nivolumab 3 mg/kg, and the median PFS was 4.9–10.6 months [103]. Thus, given also the positive results achieved by the same combination in advanced melanoma patients [4, 8], a Phase III trial is currently ongoing (CheckMate 227, ClinicalTrials.gov: NCT02477826) aiming to evaluate the OS of NSCLC patients receiving first-line nivolumab monotherapy, or nivolumab in combination with ipilimumab or chemotherapy, versus chemotherapy alone.

Other anti-PD1 and anti-PD-L1 compounds are currently under investigation as single agents or in combination for the treatment of NSCLC. Among the anti-PD-1 compounds, pembrolizumab (Keytruda®; Merck Sharp & Dohme Corp., Kenilworth, NJ, USA) was demonstrated to prolong OS compared to docetaxel, either at the dose of 2 (HR 0.71, 95% CI 0.58–0.88, P=0.0008) or 10 mg/kg (HR 0.61, 95% CI 0.49–0.75, P<0.0001) [51]. It has been approved by the FDA for the treatment of advanced NSCLC in October 2015. Results from Phase I and II trials are currently available about the role of the anti-PD-L1 compounds atezolizumab (or MPDL3280A) and durvalumab (or MEDI4736) in the treatment of NSCLC. In particular, results from the randomized Phase II trial POPLAR showed longer OS for atezolizumab compared to docetaxel (HR 0.73, 95% CI 0.53–0.99, P=0.04), in NSCLC patients after failure of a first-line platinum-based therapy. Moreover, the OS improvement correlated with PD-L1 expression[104]. No trials are currently available comparing efficacy and safety of these compounds.

Table 2 - Main trials evaluating nivolumab in NSCLC patients, from Phase I to Phase III trials, and preliminary results of ongoing trials.

Trial	Phase and line	Treatment	Patients	Findings
Gettinger et al [9]	Phase I Pretreated NSCLC	Nivolumab, q2w: - 1 mg/kg - 3 mg/k - 10 mg/kg	129 pts	ORR: 17%. ORR by dose: 3% (Nivo 1mg/kg), 24% (Nivo 3mg/kg) and 20% (Nivo 10gm/kg) Higher ORR in heavy smokers (>5 pack/years) Estimated duration of response: 17 m. Long lasting SD (≥24weeks): 10% Median OS: 9.9 months (95% CI, 7.8 to 12.4); Nivo 3 mg/Kg OS: 14.9 m; Nivo 1- or 10-mg/Kg OS: 9.2 m
Rizvi et al [2] CheckMate 063	Phase II 3rd line SqNSCLC	Nivolumab 3 mg/kg, q2w	117 pts	Response: PR=14.5% (95% CI 8.7-22.2); SD=26% (95% CI, 18-35) Median duration of response: not reached (95% CI, 8.3 m – N/R); median duration of SD: 6 m (4.7-10.6) Median OS: 8.2 m (95% CI, 6.1-10.9)
Brahmer et al[3] CheckMate 017	Phase III 2nd line SqNSCLC	Nivolumab *vs* Docetaxel	135 pts *vs* 137 pts	ORR: Nivolumab 20% (95% CI, 14-28) *vs* Docetaxel 9% (95% CI, 5-15) (p=0.008) Median OS: Nivolumab 9.2 m (95% CI, 7.3-13.3) *vs* Docetaxel 6 m (95% CI, 5.1-7.3) Risk of death 41% lower with Nivolumab (HR=0.59; 95% CI, 0.44-0.79; p<0.001)
Borghaei et al [5] CheckMate 057	Phase III 2nd line Non-SqNSCLC	Nivolumab *vs* Docetaxel	287 pts *vs* 268 pts	ORR: Nivolumab 19% (95% CI, 15-24) *vs* Docetaxel 12% (95% CI, 9-17) (p=0.02) Median OS: Nivo 12.9 m (95% CI, 9.7-15) *vs* Docetaxel 9.4 m (95% CI, 8.1-10.7) Risk of death 27% lower with Nivolumab (HR=0.73; 95% CI, 0.59-0.89; p=0.002)
Gettinger et al [36] CheckMate 012	Phase I 1st line NSCLC	Nivolumab 3 mg/kg, q2w	52 pts	*Ongoing*. Clin Trial Gov: NCT01454102 (*CheckMate 012*) *[Safety study of Nivolumab in combination with Cis/Gem, Cis/Pem, Carbo/Paclitaxel, Bevacizumab maintenance, Erlotinib, Ipilimumab or as monotherapy in pts with stage IIIB/IV NSCLC]* Nivolumab cohort: ORR=21%. Median duration of response: not reached (NR; range, 7.6+, 85.6+ weeks) Median OS: 98.3 weeks (range, 1.0-104.4+)

Table 2 - Main trials evaluating nivolumab in NSCLC patients, from Phase I to Phase III trials, and preliminary results of ongoing trials. *(Continued)*

Trial	Phase and line	Treatment	Patients	Findings
Rizvi et al [103] Checkmate 012	Phase I 1st line NSCLC	Nivolumab + Ipilimumab *(multiple doses)*	148 pts *(4 cohorts)*	*Ongoing*. Clin Trial Gov: NCT01454102 (*CheckMate 012*) *[Safety study of Nivolumab in combination with Cis/Gem, Cis/ Pem, Carbo/Paclitaxel, Bevacizumab maintenance, Erlotinib, Ipilimumab or as monotherapy in pts with stage IIIB/ IV NSCLC]* Nivo+Ipi cohort: ORR: 13–39%; median PFS: 4.9-10.6 m
Carbone [102]	Phase III 1st line PDL1+ NSCLC	Nivolumab *vs* ICC	Est. tot: 535 pts	*Ongoing*. Clin Trial Gov: NCT02041533 (*CheckMate 026*) Primary objective: PFS with Nivolumab *vs* ICC in pts with strong PD-L1 expression
ClinTrial.gov NCT02477826 CheckMate 227	Phase III 1st line NSCLC	Nivolumab *vs* Nivo+Ipi *vs* Nivo+ChT *vs* ChT	Est. tot: 1980 pts	*Ongoing*. Clin Trial Gov: NCT02477826 *(CheckMate 227)* An open-label, trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum-doublet Chemotherapy *vs* platinum doublet chemotherapy in subjects with stage IV NSCLC

Notes: Docetaxel dose in Phase III trials was 75 mg/m^2*; if not otherwise specified, nivolumab dose should be intended as 3 mg/kg, q2w.*

Abbreviations: NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; RCC, renal cell carcinoma; Ipi, ipilimumab; SqNSCLC, squamous NSCLC; ORR, overall response rate; SD, stable disease; CI, confidence interval; OS, overall survival; PR, partial response; N/R, not reported; HR, hazard ratio; PFS, progression-free survival; ICC, investigator's choice chemotherapy; ChT, chemotherapy; q2w, biweekly; Cis, cisplatin; Gem, gemcitabine; Pem, pemetrexed; Carbo, carboplatin; m, months; pts, patients.

Radiological evaluation and immune-related unconventional pattern of response

In the previous Phase I–III trials, the efficacy of nivolumab has been evaluated using the Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1) guidelines [105], which are currently considered the gold standard. Nevertheless, the kinetics of response of new immunomodulatory compounds may differ from that of chemotherapy. Due to their mechanism of action, checkpoint inhibitors such as nivolumab can lead to tumor infiltration by activated T-cells, which can sometimes radiologically appear as an increased tumor burden soon after the start of treatment[106]. This "pseudo-progression" can eventually be followed by tumor response, in a time frame ranging from 6 weeks to 6 months. Since radiological features are not currently available to definitively discriminate pseudo-progression from real tumor spread, treatment continuation beyond radiological progression can be considered for clinically stable patients[106]. Moreover, taking into account these particular features, new guidelines for response evaluation of immune therapy have been proposed [106].

An unconventional pattern of response, described as RECIST v1.1-defined progressive disease followed by PR or SD as defined per protocol, was described in a relatively low percentage of NSCLC patients treated with nivolumab. Across the Phase II and III trials, ~3%–7% of patients experienced an unconventional response. In particular, out of 117 highly pretreated patients who received nivolumab in the Phase II trial [2, 37], 22 patients were treated beyond progression, and four (3.4% of the total) met criteria for unconventional benefit. This proportion was slightly higher in the two Phase III trials: an unconventional response was seen in nine (6.8%) out of 131 nivolumab-treated squamous NSCLCs (28 patients treated beyond progression)[3] and in 16 (5.5%) out of 292 nivolumab-treated non-squamous NSCLCs (71 patients treated beyond progression) [5].

Predictive value of PD-L1 expression and emerging predictors of response to anti-PD-1 therapy

In advanced NSCLCs, nivolumab monotherapy achieves RRs of ~20%[3, 5]. Therefore, predictive factors are desirable both to select patients who can more likely benefit from anti-PD-1 treatment and for economic reasons.

Various trials, evaluating different PD-1/PD-L1 pathway inhibitors in different tumor types, have described conflicting results about the role of PD-L1 expression on tumor cells in predicting the response to treatment. Therefore, a large meta-analysis (20 trials; 1,475 patients) was conducted in order to explore the role of PD-L1 as predictive factor [55]. Among the overall population (including patients with melanoma, NSCLC, and genitourinary cancer), treated with either a PD-1 or a PD-L1 inhibitor, a significantly higher RR was described for PD-L1-positive patients, compared to the PD-L1-negative patients (ORR: 34.1% vs 19.9%, P<0.0001). The difference was also significant in the subgroup of patients treated with nivolumab (absolute difference: 16.4%, 95% CI 10.0–22.7, P<0.0001) and among patients with NSCLC (absolute difference: 8.7%, 95% CI 1.1–15.5, P=0.02) [107]. However, this study also pointed out that a non-negligible proportion of PD-L1-negative patients still respond to anti-PD-1 or anti-PD-L1 treatments.

For nivolumab-treated NSCLC patients, available data are still controversial so far (**Table 3**). Results from a non-randomized subset of 61 pretreatment specimens from 42 patients enrolled in the Phase I trial suggested a role for PD-L1 expression in predicting response to nivolumab, with 36% OR among PD-L1-positive patients and no OR among PD-L1-negative patients[7]. Out of the ten patients with NSCLC evaluable for PD-L1 expression in this preliminary analysis, five were PD-L1 positive, and one of them (with 10% positive tumor cells) achieved a PR with nivolumab 10 mg/kg. However, in a bigger cohort of NSCLCs, no association was seen between PD-L1 status and either ORR or OS[9]. Data from Phase III trials favored nivolumab in squamous NSCLC despite PD-L1 expression[3], while for non-squamous NSCLCs, PD-L1 expression seemed to be predictive of better nivolumab efficacy in terms of ORR, PFS, and OS [5]. Across different trials, ORs and longer DORs have been registered both in PD-L1-positive and PD-L1-negative NSCLCs, even if numerically higher among positive tumors [2, 36], and no differences have been described for different levels of PD-L1 expression (1%, 5%, or 10% positive tumor cells) [2, 3, 5, 37].

Table 3 - Correlation between PD-L1 expression and clinical response to nivolumab in NSCLC

Study	Evaluable specimens (pts n)	PD-L1 cut-off (% positive tumor cells)	Findings
Topalian 2012[7] *Phase I (melanoma, NSCLC, prostate, CRC, RCC)*	61 specimens 42 pts *(18 mel., 10 NSCLC, 7 CRC, 5 RCC, 2 prostate)*	≥ 5%	25 pos/42 pts → OR: 9 pts (36%) 17 neg/42 pts → OR: none *Data suggestive for a relationship between PD-L1 expression and OR*
Gettinger 2015 [9][40] *Phase I (prolonged FU NSCLC)*	68 pts	≥ 5%	33 pos/68 pts → ORR: 15%; median OS: 7.8 m (5.6 to 21.7) 35 neg/68 pts → ORR: 14%; median OS: 10.5 m (5.2 to 14.8) *No association between PD-L1 status and ORR or OS*
Rizvi 2015[2] *Phase II (SqNSCLC) CheckMate 063*	76 pts	≥ 1% ≥ 5% ≥ 10%	PD-L1 pos (≥1%) → ORR: 20% PD-L1 neg (<1%) → ORR: 13% PD-L1 pos (≥5%) → ORR: 24% PD-L1 neg (<5%) → ORR: 14% PD-L1 pos (≥ 10%) → ORR: 24% PD-L1 neg (<10%) → ORR: 14% *OR numerically higher in PD-L1 positive NSCLCs; No differences among different levels of PD-L1 expression*
Brahmer 2015[3] *Phase III (SqNSCLC) CheckMate 017*	225 pts (117 received Nivolumab)	≥ 1% ≥ 5% ≥ 10%	PD-L1 pos (≥1%) → ORR: 17% PD-L1 neg (<1%) → ORR: 17% PD-L1 pos (≥5%) → ORR: 21% PD-L1 neg (<5%) → ORR: 15% PD-L1 pos (≥10%) → ORR: 19% PD-L1 neg (<10%) → ORR: 16% *PD-L1 expression has no predictive or prognostic value; Nivolumab is more effective than docetaxel despite PD-L1 level*
Borghaei 2015 [5] *Phase III (Non-SqNSCLC) CheckMate 057*	455 pts (231 received Nivolumab)	≥ 1% ≥ 5% ≥ 10%	PD-L1 pos (≥1%) → ORR: 31% PD-L1 neg (<1%) → ORR: 9% PD-L1 pos (≥5%) → ORR: 36% PD-L1 neg (<5%) → ORR: 10% PD-L1 pos (≥10%) → ORR: 37% PD-L1 neg (<10%) → ORR: 11% *Strong predictive association between PD-L1 expression and outcome (ORR, PFS, OS) at all expression levels*
Rizvi WCLC 2015[103] *Phase I (NSCLC) CheckMate 012*	113 pts (Nivo + Ipi)	≥1%	PD-L1 pos (≥1%) → ORR: 8-48% (across different dose regimens[§]) PD-L1 neg (<1%) → ORR: 0-22% (across different dose regimens[§]) *Clinical activity was observed regardless of tumor PD-L1 expression; Preliminary evidence of greater activity in ≥1% PD-L1 positive tumors*

Note: *[a]Dose regimens included: nivolumab 1 mg/kg + ipilimumab 1 mg/kg, q3w; nivolumab 1 mg/kg, q2w + ipilimumab 1 mg/kg, q6w; nivolumab 3 mg/kg, q2w + ipilimumab 1 mg/kg, q12w; nivolumab 3 mg/kg, q2w + ipilimumab 1 mg/kg, q6w.*
Abbreviations: NSCLC, non-small-cell lung cancer; pts, patients; pos, positive; CRC, colorectal cancer; RCC, renal cell carcinoma; OR, objective response; neg, negative; FU, follow-up; ORR, overall response rate; PD-L1, programmed death 1 – ligand 1; PFS, progression-free survival; OS, overall survival.

The predictive role of PD-L1 expression has also been investigated in trials evaluating other anti-PD-1 compounds, such as pembrolizumab [51, 56]. In the Phase II/III study Keynote-010, PD-L1-positive (ie, PD-L1 expression ≥1% of tumor cells) NSCLC patients treated with pembrolizumab achieved a longer median OS compared to those receiving docetaxel (pembrolizumab 2 mg/kg: 10.4 months; pembrolizumab 10 mg/kg: 12.7 months; docetaxel 75 mg/m^2: 8.5 months). This survival advantage was higher for patients with ≥50% of PD-L1-positive tumor cells, despite the dose of pembrolizumab they received (HR 0.54 for pembrolizumab 2 mg/kg vs docetaxel, 95% CI 0.38–0.77, P=0.0002) [51].

Most nivolumab trials evaluated PD-L1 expression retrospectively on archival tumor samples, using an automated immunohistochemical assay (Dako Denmark A/S, Glostrup, Denmark). Different assays are currently available for the evaluation of PD-L1 expression, but an FDA blueprint project is ongoing to solve the differences between the registered kits[108, 109]. Unfortunately, the population tested is heterogeneous, and the PD-L1 expression in tumors seems to be heterogeneous [108]. This makes the interpretation of current data uncertain. However, the absence of univocal results suggests that PD-L1 expression might not be the only predictor of response to immune checkpoint inhibitors[109].

Recent data support the hypothesis that tumor's mutation burden could influence the response to PD-1 inhibitors. In fact, the efficacy of PD-1 inhibitors such as nivolumab is based on the ability of T-cells to recognize tumor-related antigens that are presented on the tumor cell surface by major histocompatibility complexes (**Figure 2**). In particular, neo-antigens (ie, neo-epitopes deriving from tumor-specific DNA mutations) seem to play an important role in tumor immune control[100], as suggested by the sporadic observation of systemic tumor response after local radiotherapy [110]. The likelihood of formation of neo-antigens that can be recognized by host T-cells is expected to be higher in tumors with a high mutational load, in particular if this is higher than ten somatic mutations per megabase pair (corresponding to 150 nonsynonymous mutations within expressed genes) [100].

Among different tumor types, there is high variability in mutation frequency, but differences can also be seen within the same tumor type[111, 112]. For NSCLCs, substantial differences have been described between smokers and never smokers both in terms of mutational burden and affected genes [113]. Smoking-induced lung cancers are characterized by a higher number of mutations per megabase pair compared to tumors of never smokers [112, 114, 115]. In particular, Govindan et al described a median of 10.5 mutations per megabase pair (range: 4.9–17.6) in smokers and a median of 0.6 (range: 0.6–0.9) in never smokers[116]. Recently, Rizvi et al have demonstrated a significantly improved efficacy of anti-PD-1 treatment for NSCLCs with a high nonsynonymous mutation burden, in terms of ORR, durable clinical benefit (ie, PR or SD lasting ≥6 months), and PFS [112]. Moreover, the benefit was greater for tumors harboring the "smoking signature" (ie, transversion-high [TH])[113] compared to those with transversion-low (TL) tumors (ORR: TH 56% vs TL 17%, P=0.03; durable clinical benefit: TH 77% vs TL 22%, P=0.004; PFS: TH not reached vs TL 3.5 months, P=0.0001) [112]. Lastly, recent evidence that tumors with mismatch-repair deficiency achieve higher ORR and survival compared to mismatch-repair-proficient ones seems to support the hypothesis of a role for tumor mutation load and neo-antigens in predicting the response to anti-PD-1 treatments [117, 118].

Safety and tolerability

In general, nivolumab is well tolerated (**Table 4**), and patients' performance status has been reported not to affect treatment tolerability[101]. In two Phase III trials, nivolumab was compared to docetaxel and was found to induce fewer grade 3–4 events than chemotherapy (7%–10% vs 54%–55%, respectively) [3, 5]. Across different trials [2, 3, 5, 9], treatment-related adverse events of any grade were reported in 58%–74% of the patients. The most frequent ones were fatigue, decreased appetite, and asthenia. Grade 3 or 4 adverse events were reported in 7%–17% of the patients, and the most common event was fatigue. No clear relationship between the occurrence of events and dose level or treatment duration was found [3, 9].

Table 4 - Most common nivolumab-related immune-mediated adverse events and reported frequency in the main clinical trials

Study	Pts (n)	Pneumonitis		Diarrhea		Hypothyroidism		Skin toxicity		Renal toxicity	
		Any grade	*Grade 3-4*	*Any grade*	*Grade 3-4*	*Any grade*	*Grade 3-4*	*Any grade*	*Grade 3-4*	*Any grade*	*Grade 3-4*
Gettinger 2015 [9] *Phase I (Prolonged FU NSCLC)* NCT00730639	129 NSCLC	8 (6%)	3 (2%)	13 (10%)	1 (1%)	N/R	N/R	*Rash*: 9 (7%)	None	N/R	N/R
Rizvi 2015 [2] *Phase II (SqNSCLC) CheckMate 063* NCT01721759	117 NSCLC	6 (5%)	4 (3%)	12 (10%)	3 (3%)	3 (3%)	None	*Rash*: 13 (11%)	1 (1%)	4 (3%)	None
Brahmer 2015 [3] *Phase III (SqNSCLC) CheckMate 017* NCT01642004	131 NSCLC Nivo	6 (5%)	1 (1%)	10 (8%)	None	5 (4%)	None	*Rash*: 5 (4%)	None	*Creatinine Increase* 4 (3%) *Nephritis* 1 (1%)	None 1 (1%)
Borghaei 2015[5] *Phase III (Non SqNSCLC) CheckMate 057* NCT01673867	287 NSCLC Nivo	8 (3%)	3 (1%)	22 (8%)	2 (1%)	19 (7%)	None	*Rash*: 27 (9%)	1 (<1%)	*Creatinine Increase* 5 (2%) *Renal failure: 1* (1%)	None None

Note: Data are presented as n (%).
Abbreviations: pts, patients; FU, follow-up; NSCLC, non-small-cell lung cancer; N/R, not reported.

irAEs were reported in approximately half of NSCLC patients treated with nivolumab across different trials. The most common irAEs were skin toxicity (5%–16%, consisting mainly in rash and pruritus), gastrointestinal events (8%–12%), and pneumonitis (3%–6%), and in most cases, they were of low grade.[2, 3, 9]. Other less common irAEs included endocrinopathies (4%–7%), elevation of blood liver function parameters (1%–3%), nephrotoxicity (2%–3%, mainly consisting in blood creatinine elevation), and rare infusion reactions (1%–3%)[2, 3, 5, 9].

Across different irAE categories, median time to onset (TTO) and time to resolution (TTR) ranged widely in the two Phase III trials by Brahmer et al (TTO: 0.3–17.6 weeks; TTR: 0.3–not reached)[3] and Borghaei et al (TTO: 0.1–31 weeks; TTR: 0.1–not reached)[5]. The

longest median TTO was registered for endocrine, hepatic, and pulmonary toxicities. Most of nivolumab-related adverse events were manageable with supportive care and glucocorticoids treatment, as per protocol.

Table 5 - Management of the most common irAEs

irAE	Grade 1	Grade 2	Grade 3-4
Pneumonitis	Consider discontinue treatment X-ray every 3 days If no improvement: Treat like grade 2	Discontinue treatment Start prednisone 1mg/kg/d, until resolved to grade 0-1 X-ray every 3 days If no improvement: Treat like grade 3-4	Discontinue treatment X-ray every 3 days Consider bronchoscopy/biopsy Start prednisone 1mg/kg/d, until resolved to baseline Taper prednisone in 6 weeks If no improvement (in 48 hours): Consider other immunosuppressive medication
Diarrhea	Continue treatment Start symptomatic treatment (ie loperamide)	Discontinue treatment Start symptomatic treatment (ie loperamide) Consider colonoscopy If no improvement: Treat like grade 3-4	Discontinue treatment Start prednisolone 1-2mg/kg/d until grade 0-1 Colonoscopy IV hydration and other (symptomatic) treatment of grade 3-4 diarrhea Taper prednisone in 5 weeks If no improvement: Consider infliximab
Hypothyroidism	Continue treatment Consider substitution therapy	Continue treatment Consider substitution therapy	MRI hypophyses Exclude other hormonal dysfunction Consult endocrinologist If abnormalities: Discontinue treatment Start prednisolone 1-2mg/kg/d
Skin toxicity	Continue treatment Consider local or oral treatment (ie topical steroids) If no improvement (in 2 weeks): Consider a biopsy and oral prednisone	Continue treatment Consider local or oral treatment (ie topical steroids) If no improvement (in 2 weeks): Consider a biopsy and oral prednisone	Discontinue treatment Consult dermatologist Start prednisone 1-2mg/kg/d, until resolved to grade 1 Taper prednisone in 5 weeks
Renal toxicity	Continue treatment	Discontinue treatment Check creatinine every 3 days Start prednisone 1mg/kg/d If no improvement (in 7 days): Treat like grade 3-4	Discontinue treatment Creatinine every 3 days Start prednisone 1mg/kg/d, until resolved to grade 1 Taper prednisone in 5 weeks

Note: Toxicity grading: as defined by CTCAE.
Abbreviations: irAEs, immune-related adverse events; IV, intravenous; MRI, magnetic resonance imaging; CTCAE, Common terminology criteria for adverse events.

The most common irAE leading to nivolumab discontinuation was pneumonitis [3, 9]. Grade 3–4 pneumonitis appeared in 1%–3% of the patients, and was generally manageable using corticosteroid treatment. In the trial of Borghaei et al[5], four patients (1%) experienced a grade 3–4 pulmonary adverse event (three pneumonitis; one interstitial lung disease). They were all treated with immune-modulating medication, and 75% of the events resolved completely. In the Phase II trial by Rizvi et al, all patients with pneumonitis were treated with steroids, and their median TTR was 3.4 weeks (1.6–13.4 weeks) [2]. Unresolved pneumonitis led to toxic death in three cases, all of them in the Phase I trial [9].

Diarrhea is another common irAE (8%–10%), sometimes associated with colitis [2, 3, 5, 9]. Therefore, as in the management of ipilimumab-related irAEs, with a persistent grade 2 diarrhea, a sigmoidoscopy or colonoscopy could be considered to rule out colitis [119]. Nevertheless, a grade 3–4 colitis was only reported in <1% of the patients overall. These patients improved after treatment with either supportive care or immunosuppressive therapy. When there is no improvement in 48–72 hours, infliximab could be an alternative [119].

Most commonly reported endocrine irAEs are thyroid impairments, such as hypothyroidism [2, 3, 5]. Hypophysitis has not been reported. TTR was not reached for endocrinopathies in both Phase III trials [3, 5], with a proportion of patients requiring prolonged substitution therapy with thyroid hormones. No grade 3 or 4 events were described in patients treated with nivolumab.

Treatment-related deaths were reported in two trials. In the Phase I trial by Gettinger et al [9], three cases of treatment-related deaths were described, associated with pneumonitis. Two of the patients had unresolved grade 4 pneumonitis, and the other one, grade 5. Rizvi et al [2] described two nivolumab-related deaths. One of the patients had rapid tumor progression and bronchial obstruction. An inflammatory component caused by nivolumab could not be ruled out because a bronchoscopy or autopsy was not performed. The second patient died of ischemic stroke 41 days after the only dose of nivolumab he got. Both these patients had multiple comorbidities.

In general, grade 1 or 2 irAEs are treated symptomatically (eg, loperamide for diarrhea), and discontinuation is not always necessary. For grade 3 and 4 irAEs, the treatment with nivolumab should be discontinued, and steroids (or other immunosuppressive therapy) should be started. For symptomatic endocrinopathy, substitution therapy might be required (Table 5) [119].

Other anti-PD1 and anti-PD-L1 compounds, such as pembrolizumab, showed a comparable safety pattern. No trials are currently available comparing the safety of these compounds [39].

Patient-focused perspectives: QoL and patient-reported outcomes

Given the peculiar spectrum of immune-related side effects among nivolumab-treated patients, the evaluation of their QoL is as relevant as the drug's clinical activity to make a comprehensive comparison with standard treatments. Few data are currently available, which suggest a good QoL for patients treated with nivolumab. During the 2015 ASCO meeting, patient-reported outcomes from subjects with advanced melanoma,

treated with either nivolumab or dacarbazine in CheckMate 066 trial, were reported. QoL questionnaire completion rates were 70% in the nivolumab arm and 64.9% in the dacarbazine arm. No improvement from basal QoL was described for dacarbazine-treated patients. On the contrary, nivolumab-induced QoL improvements from week 7 to week 61, registered with EuroQoL-Five Dimension questionnaire (EQ-5D), utilities and visual analog scale (VAS) scores [120]. Similarly, in CheckMate 067 trial, nivolumab led to early QoL improvements compared to ipilimumab [121]. Initial data are also available for nivolumab–ipilimumab combination regimens. These show that quality of life can be maintained at a similar level as with ipilimumab alone [121, 122].

For NSCLC, the only data available so far come from CheckMate 017 trial. In this study, the QoL questionnaire completion rates were 71.9% (97/135 patients) for the nivolumab arm and 64.2% (88/137 patients) for the docetaxel control group. A significant and progressive improvement in QoL (EQ-5D and EQ-VAS scores) was observed for subjects receiving nivolumab during the first year of treatment. EQ-VAS score was statistically higher than baseline at weeks 12, 20, 36, and 48 ($P \leq 0.05$), and similar results have been observed with EQ-5D index. Conversely, QoL for patients in the docetaxel arm showed no differences from baseline during their shorter treatment period [123]. Results from CheckMate 057 trial are still awaited.

Conclusion and future perspectives

In the recent years, new immune-modulating agents have emerged as effective treatments for the management of different tumors. In particular, nivolumab has been demonstrated to achieve a survival improvement over chemotherapy in patients with advanced NSCLC[3, 5] with a fraction of long-term survivors and a manageable toxicity profile. Given these striking results, nivolumab has recently been approved in the US and in Europe as second-line monotherapy for metastatic NSCLCs, of both squamous and non-squamous histologies. However, many questions are still open. Patients' selection is currently one of the biggest issues, both for treatment optimization and economic reasons. PD-L1 expression by tumor cells seems not to be sufficient to discriminate responders versus nonresponders, and new predictive factors are now under investigation. Tumor's mutational burden and neo-antigens are emerging as promising predictive factors [100, 112] and new diagnostic techniques are emerging to allow fast DNA sequencing, such as next-generation sequencing[124]. However, their applicability in clinical practice still has to be defined together with conclusive data of ongoing trials. The role of nivolumab in the treatment of NSCLC in other clinical settings still has to be defined. A number of ongoing trials are currently investigating its efficacy as first-line and adjuvant therapy. The use of nivolumab in combination with other systemic agents is promising, in particular when combined with other immune checkpoint inhibitors. Finally, the duration of administration of the checkpoint inhibitors is not yet defined. Studies addressing this issue are ongoing. Immunotherapy is opening new perspectives for the treatment of lung cancer, giving new effective options for this highly fatal disease, and new results from the ongoing trials are awaited in the next years.