



Nivolumab in the treatment of metastatic squamous non-small cell lung cancer: a review of the evidence

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Abstract: Progress in the treatment of patients with advanced stage squamous cell non-small cell lung cancer (NSCLC) has been limited. An improvement in the understanding of tumor immunosurveillance has resulted in the development of the immune checkpoint inhibitors such as nivolumab. Nivolumab (Opdivo®), a human immunoglobulin (Ig)G4 anti-programmed death (PD)-1 monoclonal antibody, was the first PD-1 inhibitor approved in the treatment of patients with advanced stage squamous cell NSCLC following platinum-based chemotherapy. CHECKMATE 017, a randomized phase III study of second-line nivolumab *versus* docetaxel, significantly improved overall survival (OS), progression-free survival (PFS), patient reported outcomes and the safety and tolerability favored patients treated with nivolumab. The ligand (PD-L1) expression did not predict for outcome. In this paper, we review the role of nivolumab in the treatment of NSCLC with particular attention on recent studies, ongoing combination studies, toxicity profile, current and potential predictive biomarkers.

Keywords: anti-programmed death-1, immunotherapy, nivolumab, non-small cell lung cancer

Introduction

Although the field of immune-oncology has been ongoing for more than a decade, only more recently has it generated great interest with the efficacy of immune checkpoint inhibitors (ICI). Ipilimumab, a cytotoxic T-cell Lymphocyte Antigen 4 (CTLA4) inhibitor, was amongst the first ICI to be approved by the United States (US) Food and Drug Administration (FDA), and this was subsequently followed by other ICIs such as antibodies against both programmed-cell death-protein 1 (PD-1) and its ligand (PD-L1). The ICIs have been shown to be effective in a range of hematological and solid tumors, including melanomas, non-small cell lung cancer (NSCLC), renal cell carcinoma and lymphomas [Sundar *et al.* 2015]. Nivolumab (BMS-936558), an anti-PD-1 antibody, was the first in its class to be approved by the US FDA in the second-line treatment of patients with advanced stage NSCLC (both squamous [Brahmer *et al.* 2015] and nonsquamous [Borghaei *et al.* 2015] histologies) after progression on platinum-based chemotherapy. Nivolumab is a human immunoglobulin (Ig)G4 anti-PD-1 monoclonal antibody. It acts

by binding to PD-1, an inhibitory co-receptor expressed on antigen-activated T cells, thus preventing interaction with PD-L1, resulting in the loss of inhibitory signals in T cells, and tumor recognition by cytotoxic T cells and thus restoring T-cell function (Figure 1) [Wang *et al.* 2014]. In this article, we review the current standard of care for treatment of squamous NSCLC, the role of nivolumab in its treatment, toxicities and management of treatment-related adverse events.

Treatment of squamous non-small cell lung cancer

Adenocarcinoma and squamous cell carcinoma (SCC) histologic subtypes comprise 60–70% and 10–20% of NSCLC, respectively [De la Cruz *et al.* 2011]. The survival of patients with adenocarcinoma has improved. Patients with NSCLC adenocarcinoma treated with agents targeting tumor-specific oncogenes had a median survival of 3.5 years [Kris *et al.* 2014]. However, unlike adenocarcinoma, therapeutic progress in SCC of the lung has lagged, in part due to the paucity of relevant oncogenic drivers that can inform

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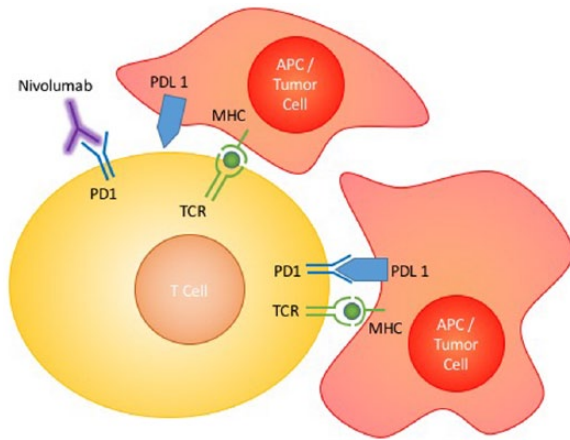


Figure 1. Mechanism of action of nivolumab.

The TCR signaling pathway is a major component of immune defense against tumors. Under normal circumstances, TCR recognition of the MHC on APCs will trigger a cascade of events causing activation of T cells and thus immune response against tumor cells. This signal is inhibited by tumor cells with activation of the PD-1/PD-L1 inhibitor co-signaling pathway, which ameliorates T-cell activation. Nivolumab acts by binding onto the PD-L1 on T cells, thus preventing inhibitor co-signaling and restoring T-cell activation.

APC, antigen presenting cell; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death-1 ligand; TCR, T-cell receptor.

treatment. This evidence suggests that new drugs for metastatic squamous NSCLC are needed. The treatment of nonsquamous NSCLC has seen significant progress in the past decade with the identification of molecular subtypes [Kumarakulasinghe *et al.* 2015]. Data from the Cancer Genome Atlas Research Network (TCGA) showed significant differences in genetic profiles between the two most common histological subtypes of lung cancer, adenocarcinoma and SCC [Cancer Genome Atlas Research, 2012, 2014]. Overall, 62% of lung adenocarcinomas harbored known activating mutations in driver oncogenes, including mutations in the epidermal growth factor receptor (EGFR) gene and echinoderm microtubule-associated protein-like 4 – anaplastic lymphoma kinase (EML4-ALK) and ROS1 gene fusion and the use of tyrosine kinase inhibitors (TKIs) towards target proteins [Cancer Genome Atlas Research, 2014]. However similar driver mutations are uncommonly observed in SCCs [Cancer Genome Atlas Research, 2012]. As such, platinum-based doublet chemotherapy, such as carboplatin/ paclitaxel or gemcitabine/ cisplatin has remained the mainstay of first-line treatment of squamous NSCLC [Ang *et al.* 2015]. Recently, the addition of necitumumab, a

second-generation EGFR monoclonal antibody, showed significant improvement in progression-free survival (PFS) (5.7 *versus* 5.5 months, 95% CI 0.74–0.98, $p = 0.02$) and overall survival (OS) (11.5 *versus* 9.9 months, 95% CI 0.74–0.96, $p = 0.01$) when added to the platinum doublet of cisplatin-gemcitabine in patients with metastatic SCC lung [Thatcher *et al.* 2015]. Further analysis of correlation between EGFR expression by IHC scoring and FISH analysis suggest possible predictive values towards response, although this will need to be further validated. Nonetheless, necitumumab is the first drug that has been approved in first-line treatment for SCC lung since the use of platinum-based doublet therapy in the past decade.

Traditionally the median OS in patients treated with second-line therapy for advanced NSCLC is about 8 months, with docetaxel the most frequent chemotherapy of choice [Shepherd *et al.* 2000; Kim *et al.* 2008]. Nonetheless, recent pooled analysis from various second-line docetaxel studies have suggested that patients with squamous histology tend to do worse than those with nonsquamous histologies, amidst already dismal survival improvements [Torri *et al.* 2015]. In a phase III study of second-line docetaxel and ramucirumab *versus* docetaxel (REVEL study), OS favored the combination arm with an OS of 10.5 *versus* 9.1 months [hazard ratio (HR) 0.86, 95% CI 0.75–0.98]. In the 26% of patients with SCC, the HR for OS was 0.761 (95% CI 0.606–0.957) [Garon *et al.* 2014]. In a phase III study of docetaxel and nintedanib *versus* docetaxel, among patients with SCC lung (42%), the addition of nintedanib was associated with a PFS of HR 0.77 (95% CI 0.62–0.96), and an OS of HR 1.01 (95% CI 0.85–1.21, $p = 0.891$) [Reck *et al.* 2014]. In a phase III study of second-line afatinib *versus* erlotinib, the median PFS was 2.6 *versus* 1.9 months (HR 0.81, 95% CI 0.69–0.96, $p = 0.0103$), and OS was 7.92 *versus* 6.77 months (HR 0.808, 95% CI 0.691–0.946, $p = 0.0077$) [Soria *et al.* 2015]. In these studies, the survival benefit, whilst statistically significant, is only modest and novel therapeutic approaches are needed. The success of ICI in melanoma has led to its use in other solid tumors including NSCLC.

Nivolumab in lung cancer

Nivolumab (Opdivo®, Bristol Myers Squibb, USA) was the first ICI to be approved by the US FDA in the treatment of SCC lung in March

2015, with its approval extended to lung cancers of nonsquamous histologies in October 2015 [Sundar *et al.* 2015]. In addition, nivolumab has been approved by the US FDA for the following indications: unresectable or metastatic melanoma, classical Hodgkin's lymphoma after failure of more than two treatment lines, second-line treatment of advanced renal cell carcinoma, and in combination with ipilimumab, a CTLA-4 inhibitor, in metastatic melanoma irrespective of BRAF status.

Pembrolizumab (Keytruda®, Merck, USA), another anti-PD-1 agent, was approved by the US FDA in October 2015 for use in a second-line setting post platinum-based chemotherapy for patients with metastatic NSCLC whose tumors express PD-L1.

The first in-human studies of nivolumab carried out were basket trials carried out in refractory solid tumors, of which 15.4% patients (six out of 39) had NSCLC [Topalian *et al.* 2012]. Patients on the study received a single dose of nivolumab at doses ranging from 0.3–10 mg/kg with provision for a repeat dose at 3-month intervals for patients who derived clinical benefit. Although drug efficacy was not the primary endpoint in this phase I trial, significant tumor regression was seen in one of the six patients with NSCLC, despite the fact that lung cancers were not known to be classically immunogenic compared with tumors like renal cell carcinomas and melanomas. The drug was well tolerated and maximum tolerated dose (MTD) was not reached, with only one patient developing the serious adverse event (SAE) of inflammatory colitis [Brahmer *et al.* 2010].

Based on these results, a dose-expansion cohort of patients with NSCLC were enrolled into trial. Of these 129 patients enrolled, 54 patients (41.2%) had SCC lung. The overall response rate (ORR) was 17% across all cohorts, and median OS was 9.9 months, with median survival in the 3 mg/kg cohort performing best at 14.9 months [Gettinger *et al.* 2015]. This was similar for both patients with squamous and nonsquamous histology. PD-L1 expression status did not appear to predict for tumor response, and subgroup analysis suggest that better responses were seen in former and current smokers (ORR 30% in patients with smoking history of more than 5 pack-years *versus* 0% in patients with smoking history of 5 pack-years or less) [Gettinger *et al.* 2015a]. Based on the promising results,

subsequent phase II studies with nivolumab at a dose of 3 mg/kg every 2 weeks were conducted.

In a phase II single-arm study (CHECKMATE 063), 117 patients with advanced stage squamous cell NSCLC were treated with nivolumab in third-line and beyond. The ORR was 14.5%, 26% of patients had stable disease and the 6-month and 12-month PFS was 25.9% and 20.0% [Rizvi *et al.* 2015]. These results were noteworthy given 65% of patients were previously treated with three or more lines of systemic therapy, and in 61% of patients, disease progression was the best response to the most recent treatment. Updated survival results presented recently reported an OS of 8.2 months and 1-year OS rate of 41% [Horn *et al.* 2015]. In a Japanese phase II study (ONO-4538-05), of patients with advanced stage SCC lung ($n = 35$) and nonsquamous lung cancer ($n = 76$) treated with nivolumab, the ORR was 25.7% in the SCC group. In addition, the disease control rate (DCR) of 54.3% and the PFS of 4.2 months. The OS was not reached [Nakagawa *et al.* 2015] (Table 1). In another phase II study conducted at community research sites (CHECKMATE 153, CA209-153) patients with advanced stage NSCLC were treated with nivolumab till progression or unacceptable toxicities compared with being treated for a maximum of 1 year, then discontinuation with an intention to restart nivolumab at progression. Of the 824 patients enrolled, 227 patients (28%) had a SCC histologic subtype. The ORR and stable disease at first assessment was 13% and 50%, respectively, in patients with squamous cell NSCLC [Hussein *et al.* 2015]. While the second study involved patients with both squamous and nonsquamous subtypes, both phase II studies supported that nivolumab was effective in patients with SCC lung compared with historical outcomes of patients on conventional chemotherapy. As such, further phase III trial was undertaken for patients with SCC lung.

In a phase III study of nivolumab *versus* docetaxel in 272 patients with advanced SCC lung (CHECKMATE 017), the study was terminated early on the recommendation of the independent data and safety monitoring committee as pre-specified interim analysis succeeded in showing an improvement in their primary endpoint of OS. The OS with nivolumab and docetaxel was 9.2 and 6.0 months, respectively (HR 0.59, 95% CI 0.44–0.79, $p < 0.001$) [Brahmer *et al.* 2015]. Furthermore, the ORR and PFS favored nivolumab (20% *versus* 9%,

Table 1. Trials of nivolumab in SCC lung.

Phase	Author	Line of treatment	Sample size	ORR (%)	PFS (months) (95% CI)	OS (months) (95% CI)	Limitations
I	Topalian NEJM2012 [Topalian <i>et al.</i> 2012], Gettinger JCO2015 [Gettinger <i>et al.</i> 2015]	Second line and beyond	54	16.7	NA	9.2 (7.3–12.5)	Small sample size Multiple treatment lines
I	Gettinger ASCO2015 [Gettinger <i>et al.</i> 2015]	First line	13	15	NA	18.2 (CI not reported)	Small sample size First line only
II (CHECKMATE 063)	Rizvi Lancet 2015 [Rizvi <i>et al.</i> 2015]	Third line and beyond	117	14.5	1.9 (1.8–3.2)	8.2 (6.1–10.9)	Heavily pretreated population, with 20.5% of patients having 4 or more lines of previous treatment
II (ONO-4538-050)	Nakagawa JTO2015 [Nakagawa <i>et al.</i> 2015]	Second line and beyond	35	25.7	4.2 (1.5–7.1)	Not reached (12.4–not reached)	Preliminary results Small sample size Asian population Multiple treatment lines
II (CHECKMATE 153)	Hussein WLCC2015 [Hussein <i>et al.</i> 2015]	Second line or more	145	13	NA	NA	Preliminary results Study compared 1 year <i>versus</i> continuous nivolumab
III (CHECKMATE 017)	Brahmer NEJM2015 [Brahmer <i>et al.</i> 2015]	Second line	272	20	3.5 (2.1–4.9)	9.2 (7.3–13.3)	Multiple treatment lines Retrospective analysis of PD-L1 expression Compared against docetaxel whereas newer regimens such as docetaxel + ramucirumab is superior to docetaxel

CI, confidence interval; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

Table 2. Combination studies of nivolumab in non-small cell lung cancer.

Phase	Author	Line of treatment	Sample size	ORR (%) [range]	PFS (months) [range]	OS (months) [range]
I	Antonia [Antonia <i>et al.</i> 2014a]	First line with chemotherapy	56	33–57	4.1–6.1	50.5–NR
I	Rizvi [Rizvi <i>et al.</i> 2014]	EGFR+ but resistant nivolumab + erlotinib	21	19	NA	NA
I	Antonia [Antonia <i>et al.</i> 2014b]	Second line with ipilimumab	148	13–39	4.9–10.6	NR

NA, not available; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

$p = 0.008$) and HR 0.63 (95% CI 0.48–0.83, $p < 0.01$), respectively (Table 1). Again PD-L1 expression was neither prognostic nor predictive of outcomes. Lung Cancer Symptom Scale (LCSS) assessment of patients showed that patients who responded to nivolumab appeared to have a more sustained period of symptom improvement compared with patients on docetaxel. Time to first disease deterioration measured by LSCC Global Health Related Quality of Life was longer in patients treated with nivolumab compared with patients treated with docetaxel (HR 0.58, 95% CI 0.39–0.86) [Gralla *et al.* 2015]. With the positive outcome of this study, the US FDA approved nivolumab for the treatment of advanced SCC lung with progression on or after platinum-based chemotherapy. Nonetheless, certain limitations remain, including the role of PD-L1 expression as a predictive marker, that is still an area of active investigation. While nivolumab is superior to docetaxel, the efficacy of nivolumab compared with other recent active combinations such as docetaxel with ramucirumab or nintedanib remains to be seen.

Current trials are being undertaken to look at the efficacy of nivolumab compared with platinum doublet treatment in a first-line setting. CHECKMATE026 included patients with both squamous and nonsquamous NSCLC, has completed accrual and early results may be made available by 2017. In the squamous cohort, patients were randomized to either nivolumab or platinum doublet (cisplatin or carboplatin combined with either gemcitabine or paclitaxel) with the option of crossover at disease progression (Table 2).

Rationale for combination therapy

Preclinical data have suggested that combination of ICIs with chemotherapy or other

targeted therapy like anti-angiogenic drugs may have synergistic effects. Akbay and colleagues showed that PD-L1 expression may be upregulated *via* the EGFR signaling pathway [Akbay *et al.* 2013], and D’Incecco and colleagues showed that there was a significant correlation between EGFR and KRAS mutations with PD-L1 and PD-1 expression respectively [D’Incecco *et al.* 2015]. The combination of nivolumab with EGFR-mutant NSCLC is being studied in patients who are treatment naïve or have progressed on first-line EGFR TKI therapy. Preliminary results reported an ORR of 19%, 6-month PFS of 51% and 1-year OS of 73% [Rizvi *et al.* 2014].

Conventional chemotherapy occurs largely through apoptosis, which is believed to be nonimmunogenic compared with necrosis, which is more inflammatory in nature. Preclinical data have shown that combination of chemotherapy with immunotherapy may lead to more pronounced cell death due to complementary pathways in cell killing [Apetoh *et al.* 2008]. The combination of nivolumab with platinum-based doublet in the first-line setting has shown encouraging outcomes. In a phase I trial of 56 patients with NSCLC, including both squamous and nonsquamous histology, patients were treated with four cycles of nivolumab plus platinum-based doublet in four different subgroups, with continuation of nivolumab alone till progression or unacceptable toxicities. The ORR ranged from 33–57%, PFS 21–31 weeks and median OS of 50.5 weeks to not reached [Antonia *et al.* 2014b].

In vitro studies have shown anti-CTLA4 and anti-PD-1 inhibition have synergistic effects in promoting cell death. Combined PD-1 and CTLA-4 blockade has been shown to increase effector T-cell infiltration in melanoma cells, that

Table 3. Ongoing trials of nivolumab in advanced NSCLC.

Phase	Line of treatment	Control arm	Experimental arm	Clinical trial gov. number
I (CHECKMATE 012)	Second line and beyond	-	Nivolumab + ipilimumab, nivolumab + platinum doublet, nivolumab + erlotinib	NCT01454102
III (CHECKMATE 026)	First line	Platinum doublet	Nivolumab	NCT02041533
I	Second line and beyond	-	Nivolumab + EGF816 or INC280	NCT02323126
III (CHECKMATE 078)	Second line	Docetaxel	Nivolumab	NCT02613507
III (CHECKMATE 227)	First line	Platinum doublet	Nivolumab, nivolumab + ipilimumab, nivolumab + platinum doublet	NCT02477826
II (CHECKMATE 568)	First line	-	Nivolumab + ipilimumab	NCT02659059
I	First line	-	Nivolumab + ceritinib	NCT02393625

eventually leads to decreased anergy and increased activity that allows for the tumor microenvironment to shift from suppressive to inflammatory [Curran *et al.* 2010]. Encouraging preclinical data, combined with success of combination therapy in melanomas have fueled the extension of such studies in NSCLC. CHECKMATE012, a phase I trial, is currently investigating the combination of nivolumab with ipilimumab at various dose combinations. Initial results have been encouraging with ORR range from 13–39% and median PFS from 4.9–10.6 months in various treatment arms. Grade 3/4 SAEs were seen in 28% of patients, including pneumonitis, diarrhea, colitis and raised liver function, with three patient deaths deemed attributable to drug-related toxicities, including respiratory failure following colitis, pulmonary hemorrhage and toxic epidermal necrolysis in a patient with history of ulcerative colitis. [Antonia *et al.* 2014].

Adverse events

Based on the mechanism of action of nivolumab, the anticipated side effects are immune-related adverse events (irAEs). In studies of patients with NSCLC treated with nivolumab, any grade adverse events were reported in 58–85% of patients, while rates of grade 3–4 toxicities ranged from 5.7–17% (Table 3). The common side effects included fatigue (16–33%), anorexia (11%), diarrhea (8–10%) and endocrinopathies [Rizvi *et al.* 2014; Brahmer *et al.* 2015; Nakagawa *et al.* 2015].

The rate of treatment-related adverse events (TRAEs) leading to discontinuation and death is relatively low with nivolumab. In CHECKMATE 063 [Rizvi *et al.* 2015], 12% and 1.7% of patients experienced TRAE discontinuation and death, respectively, and in CHECKMATE 017 [Brahmer *et al.* 2015], it was 3% and 0%, respectively. In comparison, the rate of TRAE discontinuation and death in patients treated with docetaxel in CHECKMATE 017 was 10% and 2%, respectively. In addition, there was more neutropenia of any grade (33% *versus* 1%) and febrile neutropenia (11% *versus* 0%) in patients treated with docetaxel compared with nivolumab.

Pneumonitis was the most common irAE resulting in nivolumab discontinuation. Pneumonitis is generally mild and manageable with steroid treatment. In CHECKMATE 063, 5% of patients had pneumonitis of which 3% was grade 3 or higher. In this study, all patients responded to steroids and the median time to resolution was 3.4 weeks (1.6–13.4 weeks) [Rizvi *et al.* 2015]. In CHECKMATE 017, 5% of patients had pneumonitis (any grade) whereas no patients had pneumonitis in the docetaxel arm. In the phase I study, three patients had unresolved pneumonitis, resulting in mortality [Gettinger *et al.* 2015]. The onset of pneumonitis may be variable. In a recent report of patients with melanoma treated with nivolumab, the onset of pneumonitis was 7.4–24.3 months from treatment initiation [Nishino *et al.* 2015]. Onset can be insidious with symptoms like cough, while others developed

Table 4. Immune related adverse events (%) in patients treated with nivolumab.

Study	CHECKMATE 063 [Horn <i>et al.</i> 2015]		ONO-4538-050 [Nakagawa <i>et al.</i> 2015]		CHECKMATE 017 [Brahmer <i>et al.</i> 2015]	
	All grade	Grade 3/4	Grade 3/4	Grade 3/4	All grade	Grade 3/4
Immune related adverse events						
Skin	15.5	0	0	0	28.6	0
Gastrointestinal	11.6	0.8	1	1	5.7	0
Pulmonary	7.0	2.3	1	1	5.7	0
Endocrinopathies	6.2	0	0	0	11.4	0
Hepatitis	4.7	0.8	0	0	5.7	0
Renal injury	3.1	0	1	1	2.9	0

dyspnea and hypoxia. Radiology may show ground glass changes with reticular opacities, although consolidative changes were also observed in one patient. The diagnosis of pneumonitis may be challenging in patients, especially in those with underlying airways disease or metastases confounding underlying baseline symptoms. It may also sometimes be difficult to discern development of pneumonitis from underlying disease progression from description of symptoms alone. It is important to have a high degree of suspicion and early access to imaging as this may be useful in differentiating the etiology of worsening respiratory symptoms.

The management of irAEs include the use of steroids and in more severe cases, immunomodulatory agents such as anti-metabolite (mycophenolate mofetil), anti-tumor necrosis factor (TNF)- α antibody (infliximab) and calcineurin inhibitors (tacrolimus and cyclosporine). Choice of steroids and immunomodulatory agents are largely dependent on grade of side effects, and are summarized in Table 4 [Naidoo *et al.* 2015; Spain *et al.* 2016; Bristol-Myers-Squibb, 2016]. While the Common Terminology Criteria for Adverse Events (CTCAE) is the most common platform used to grade toxicities, there have been concerns about whether it may underestimate certain toxicities like hypophysitis. With increased understanding of irAEs, better grading systems may eventually evolve.

Role of predictive biomarkers

In this era of precision medicine, companion diagnostics such as a validated predictive biomarkers that may be able to help select for patients who are most likely to respond to treatment, is paramount in optimizing patient outcomes.

Studies involving nivolumab have collected immunohistochemical (IHC) data in terms of measurement of PD-1, PD-L1 and tumor infiltrating lymphocytes (TIL) expression levels in tumor samples for correlation with treatment outcomes. Thus far, none of the above IHC expression levels have conclusively proven to be either prognostic or predictive of response to treatment. In CHECKMATE 017, tumor expression of PD-L1 by immunohistochemistry does not seem to be predictive for OS or PFS benefit to nivolumab [Brahmer *et al.* 2015]. However in CHECKMATE 057, PD-L1+ patients treated with nivolumab was associated with an improved OS, PFS and duration of response at the predefined 1%, 5%, and 10% cut-off points [Borghaei *et al.* 2015]. These findings suggest there may be inherent differences in the tumor microenvironment between SCC *versus* nonsquamous cancer, consistent with the idea that these are two distinct diseases. Inherent challenges are present in the use of IHC expression levels, as differing antibodies and staining techniques may affect scoring. There are currently no standard criteria across various anti PD-1 and PD-L1 trials in terms of reporting of a positive expression, making it even more challenging to confirm the utility of IHC expression level with outcomes. To improve on patient selection for ICIs, other biomarkers have been explored. Tumor mutation and neo-antigen load are potentially promising predictive factors [Schumacher and Schreiber, 2015]. However, the clinical applicability of this biomarker approach remains to be defined.

Conclusion and future perspectives

The positive results of CHECKMATE 017 have established the role of nivolumab as a superior option as compared with docetaxel in the

Table 5. Overview on the treatment of immune-related toxicities, adapted from Spain and colleagues [Spain *et al.* 2016], Naidoo and colleagues [Naidoo *et al.* 2015] and product insert [Bristol-Myers-Squibb, 2016].

	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Topical steroid cream, antihistamines, can continue ICI	Initiate systemic steroids (prednisolone 0.5–1 mg/kg/day) and delay treatment until symptoms resolve to Grade 1	Hold ICI. Commence steroids (prednisolone 1–2 mg/kg/day). Dermatology consult for skin biopsy	Permanently discontinue ICI. Management as per Grade 3.
Gastrointestinal	Supportive measures, can continue ICI	Hold ICI. Commence steroids (prednisolone 0.5–1 mg/kg/day) until symptoms improve to Grade 1. If symptoms do not improve after 5 days, consider increasing steroids to 1–2 mg/kg/day.	Hold ICI. Intravenous hydration, commence steroids (prednisolone 1–2 mg/kg/day). Add infliximab 5 mg/kg if no improvement	Permanently discontinue ICI. Acute treatment as per Grade 3, consider referral to gastroenterology and surgery for opinion in management.
Pulmonary	Consider commencement of steroids (prednisolone 0.5–1 mg/kg/day)	Hold ICI. Commence steroids (1–2 mg/kg/day) until improvement. consider empiric antibiotics.	Permanently discontinue ICI. High dose steroids (IV methylprednisolone 2–4 g/day) with empirical antibiotics. Add immunomodulatory agent if no improvement after 48 h. referral to pulmonologist for consideration of bronchoscopy.	Permanently discontinue ICI. Acute management as per Grade 3, consider intensive care support
Thyroid dysfunction	Continue ICI. Monitor thyroid function	Hold ICI. Referral to endocrinology for further management	Permanently discontinue ICI. Commence steroids (Prednisolone 1–2 mg/kg), referral to endocrinology for further management	Permanently discontinue ICI. Management as per Grade 3
Hepatitis	Continue ICI. Rule out other causes of hepatitis including viral, metabolic and alcoholic causes	Hold ICI. Commence steroids (prednisolone 0.5–1 mg/kg/day) until symptoms improve to Grade 1.	Hold ICI, consider permanent discontinuation. Commence steroids as per Grade 2.	Permanent discontinue ICI. Acute treatment as per Grade 3, consider referral to hepatologist.
Renal	Can continue ICI. Supportive measures (encourage hydration, monitor renal function, medication reconciliation to avoid nephrotoxic drugs)	Hold ICI. Commence steroids (prednisolone 0.5–1 mg/kg/day)	Permanently discontinue ICI, commence steroids (prednisolone 1–2 mg/kg/day), consider high dose steroids. Referral to nephrologist for further management	Permanently discontinue ICI. Acute management as per Grade 3, consider acute hemodialysis
ICI, immune checkpoint inhibitor; IV, intravenous.				

second-line therapy in lung SCC. Studies of nivolumab in first-line settings are ongoing and results are greatly anticipated. Currently, many further studies are underway to investigate nivolumab's role both as a single agent and as combination therapy at various lines of treatment (Table 5). These studies will undoubtedly help to further define the role of nivolumab in the treatment algorithm of NSCLC. However, undefined areas remain and are actively being explored, including the role of ICIs in the adjuvant setting, in stage III following chemotherapy and radiotherapy and duration of treatment. Further studies to investigate predictive biomarkers and a better understanding of how we evaluate treatment response will further help to optimize the outcomes of patients on treatment.

In conclusion, ICI has proven benefit in the treatment of metastatic NSCLC, especially in the setting of SCC where targeted therapy with TKIs has not been particularly effective. It is currently a treatment of choice post-progression on platinum-based chemotherapy, and several studies are underway to examine its role in a first-line setting and also in combination with chemotherapy and other immunotherapeutic agents.

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