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REVIEW

Profile of nivolumab in the treatment of metastatic squamous non-small-cell lung cancer

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Abstract: Until recently, the prognosis and treatment of patients with advanced-stage squamous cell lung cancers have been limited. An improvement in the understanding of the role of the immune system in tumor immunosurveillance has led to the development of the programmed death-1 (PD-1) immune checkpoint inhibitor nivolumab (Opdivo). Nivolumab is the first PD-1 inhibitor approved for the treatment of advanced-stage squamous cell non-small-cell lung cancer following platinum-based chemotherapy. In the key Phase III trial CHECKMATE 017, a better overall survival and progression-free survival were seen in patients treated with second-line nivolumab compared with docetaxel. Programmed death ligand-1 (PD-L1) expression did not predict for outcome. In addition, nivolumab had better safety and tolerability, and led to better patient reported outcomes. Further research on the role of PD-L1 expression as a predictive biomarker should be performed, and other biomarkers that can predict the efficacy of PD-1/PD-L1 inhibitors should also be pursued. Further studies on the combination treatment are ongoing to determine the optimal role of nivolumab as monotherapy or nivolumab with other agents in non-small-cell lung cancer.

Keywords: immunotherapy, programmed death-1, PD-1, NSCLC, squamous cell, nivolumab

Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide. Squamous cell lung cancers (SCCs) make up 20%–30% of all lung cancers, representing a significant health burden.[1] In advanced-stage lung adenocarcinoma, the last 5–10 years have seen great strides in the development of molecular targeted therapies, which has changed the outlook for patients with this disease. However, until recently, treatment of patients with advanced-stage SCCs was limited. Advances in the understanding of the interaction between the immune system and tumors have led to the development of programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors targeting the immune checkpoint pathway.[2]

The standard first-line therapy for SCC is a platinum-based doublet chemotherapy without pemetrexed.[3–5] More recently, a second-generation platinum derivative, nedaplatin, in combination with docetaxel, improved outcomes compared to cisplatin/docetaxel as first-line treatment in advanced-stage SCC, with an overall survival (OS) benefit of 13 vs 11.4 months (hazard ratio [HR] 0.81, 90% confidence interval [CI] 0.67–0.98).[6] In a Phase III trial comparing weekly nab-paclitaxel with carboplatin vs 3-weekly sb-paclitaxel with carboplatin, on subset analysis in SCC, the response rate with nab-paclitaxel and sb-paclitaxel was 41% and 24%, respectively.[7] In the Phase III SQUIRE study, patients with SCC were randomized to cisplatin and gemcitabine with or without necitumumab, a second-generation recombinant human IgG1 EGFR

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antibody. The OS was longer in the necitumumab arm (11.5 vs 9.9 months; HR 0.84, 95% CI 0.74–0.96, *P*=0.01).[8]

In the second-line setting, docetaxel monotherapy is considered as a standard chemotherapy option.[9] In a recent pooled analysis of several second-line docetaxel studies (TAILOR, DELTA, and PROSE), patients with squamous histology treated with docetaxel had a poorer survival compared to patients with nonsquamous histology (OS 6.3 vs 10.9 months), suggesting that docetaxel may be less effective in squamous compared to nonsquamous lung cancer.[10] In a Phase III study of docetaxel with or without ramucirumab (REVEL), an OS benefit was seen with the addition of ramucirumab (10.5 vs 9.1 months, HR 0.86, 95% CI 0.75–0.98, *P*=0.023).[11] It has to be noted that 26% of patients had squamous cell histology. There was a significant OS benefit in the SCC subgroup with a HR of 0.761 (95% CI 0.606–0.957, *P*=0.019). In a Phase III study of docetaxel with or without nintedanib, 42% had squamous cell subtype. In the squamous cell subtype, the addition of nintedanib was associated with a progression-free survival (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). More adverse events were seen in the docetaxel and nintedanib arms.[12] In LUX-Lung 8, a Phase III study of second-line afatinib vs erlotinib, the median PFS was 2.6 vs 1.9 months (HR 0.81, 95% CI 0.69–0.96, *P*=0.0103), and OS was 7.92 vs 6.77 months (HR 0.808, 95% CI 0.691–0.946, *P*=0.0077).[13] The survival benefits seen in these studies when compared to studies with docetaxel, while statistically significant, represent modest developments in the treatment of advanced-stage SCC, a disease where little progress has been made previously. Survival remains dismal, and novel therapeutic approaches are needed.

Through research on tumor immunosurveillance, it has emerged that tumors can evade immune destruction via the dysregulation of coinhibitory or checkpoint signals.[14] In the physiologic state, PD-1, an immune checkpoint or co-inhibitory molecule expressed on activated T-cells, acts to prevent autoimmunity. The binding of PD-1 with one of its ligands, programmed death-ligand 1 (PD-L1) (or CD274, B7-H1) or PD-L2 (CD 273, B7-DC), results in downregulation of cytotoxic T-cells. Solid tumors can co-opt the PD-1/PD-L1 pathway to evade T-cell-induced antitumor response. PD-L1 is also expressed on many tumors, including 20%–65% of non-small-cell lung cancers (NSCLCs).[2,15] By inhibiting the PD-1/PD-L1 pathway with immune checkpoint inhibitors, the engagement of PD-1 with its ligands is interrupted, resulting in the loss of inhibitory signals in T-cells and leading to tumor recognition by cytotoxic T-cells.

The development of PD-1 immune checkpoint inhibitors, such as nivolumab and pembrolizumab, and the PD-L1 inhibitors atezolizumab (MPDL3280A) and durvalumab (MEDI4736), represents an important therapeutic advance in the treatment of solid tumors. Early reports and recent Phase III trials of PD-1/PD-L1 inhibitors have reported clinical activity and durable responses in patients with refractory tumors, including melanoma, renal cell cancer, Hodgkin's lymphoma, bladder cancer, and NSCLC.[16–22] Nivolumab (Opdivo, BMS) was the first immune checkpoint inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of patients with advanced-stage squamous and nonsquamous NSCLC following progression on or after platinum-based chemotherapy. In this article, we will review the role of nivolumab in the treatment of SCC of the lung.

Pharmacology of nivolumab

Nivolumab is a fully human IgG4 monoclonal antibody against PD-1, thus blocking both PD-L1 and PD-L2 binding; it binds to the PD-1 receptor with high affinity (Kd=2.6 nmol/L).[23] In in vitro experiments, nivolumab at a concentration of 0.04 μg/ml gives a PD-1 receptor occupancy of >70%.[24] In patients with advanced-stage melanoma treated with nivolumab at a dose of 0.1–10.0 mg/kg every 2 weeks for 8 weeks, the median PD-1 receptor occupancy was 64%–70%, and nivolumab may occupy PD-1 receptors for up to 3 months following dosing.[24] The IgG4 isotype, which was engineered to minimize antibody-dependent complement-cellular cytotoxicity (ADCC) as an intact ADCC, has the potential to deplete activated T-cells and tumor infiltrating lymphocytes, thereby reducing T-cell activity.[23]

The pharmacokinetics of nivolumab is linear and dose proportional in the range of 0.1–10 mg/kg, with a half-life of 17–25 days and is cleared by the reticuloendothelial system.[24] The clearance of nivolumab is increased with increasing body weight and is not significantly affected by age, sex, race, or antidrug antibodies.[25,26] Dose adjustment is not required in patients with mild hepatic impairment or in patients with mild renal impairment.[27]

Therapeutic efficacy of nivolumab

Phase I studies

A Phase I study of nivolumab was conducted in 39 patients with solid tumors in dose-escalating six-patient cohorts given as a single dose of 0.3, 1, 3, or 10 mg/kg, with a 15-patient expansion cohort at 10 mg/kg. Nivolumab was

observed to be well tolerated at the maximum planned dose of 10 mg/kg, with the occurrence of a single serious adverse event, inflammatory colitis. Of the six patients with NSCLC, one patient had a response not amounting to a partial response.[24] Nivolumab administered once every 2 weeks, at doses from 0.1 to 10.0 mg/kg, was subsequently tested in a multiple-dose trial of patients with advanced-stage solid tumors, including melanoma, NSCLC, castrate-resistant prostate cancer, renal cell carcinoma, and colorectal cancer. Nivolumab was relatively well tolerated, a maximum tolerated dose was not reached in this study; >80% of patients managed to receive a relative dose intensity of 90%. Of the 130 patients treated with nivolumab at 10 mg/kg, 8% had grade 3 or 4 adverse events, including endocrine disorders (hypophysitis, thyroiditis), diarrhea, and pneumonitis. Of the 76 patients with NSCLC, the response rate was 18%, and the progression-free rate at 24 weeks was 26%. In the squamous cell cohort (n=18), the response rate was 33%, and the progression-free rate at 24 weeks was 33%.[17]

Phase II studies

Several single-arm studies have reported on the efficacy of nivolumab in advanced-stage squamous NSCLC (Table 1). In CHECKMATE 063, a Phase II single-arm trial of nivolumab in third-line therapy and beyond, 117 patients were treated with nivolumab 3 mg/kg every 2 weeks until progression. The median age was 65 years, 73% were males, 78% had an Eastern Cooperative Oncology Group (ECOG) performance status of 1, and 83% had stage 4 disease. The patient population was highly refractory to treatment, with 65% of patients previously treated with at least three prior lines of systemic therapy, and 61% of patients had disease progression as best response to the most recent therapy. Patients received a median of six doses of nivolumab, and the median treatment duration was 2.3 months. The partial response rate was 14.5%, and 26% of patients had stable disease. The median time to response was 3.3 months and the median duration of response was not reached, suggesting that while it took some time for a response to be seen, responses were generally durable.[28] The median PFS was 1.9 months with a PFS of 25.9% at 6 months and 20.0% at 1 year. The OS was 8.2 months, and the 1-year survival was 40.8% (Table 1).

Preliminary data from two other Phase II studies have recently been presented. In a Japanese study (ONO-4538-05), nivolumab 3 mg/kg twice weekly was administered to patients with advanced-stage squamous (n=35) and nonsquamous lung cancer (n=76), who had progressed on a prior line of

Table 1 Clinical outcome in advanced-stage squamous non-small-cell lung cancer treated with immune checkpoint inhibitors

Phase	Treatment line	Sample size	ORR, %	PFS, HR (95% CI), months	PFS at 24 weeks, %	PFS rate at 1 year, HR (95% CI), %	OS, HR (95% CI), months	1-year OS rate, %	References
Nivolumab									
Phase I	Second line or more	18	33	NA	33	NA	NA	NA	Topalian et al[17]
Phase II	Third line or more	117	14.5	1.9 (1.8–3.2)	25.9	20 (12.7–28.5)	8.2 (6.1–10.9)	41	Rizvi et al[28]
	Second line	35	25.7	4.2 (1.5–7.1)	NA	NA	NR (12.4 NR)	NA	Nakagawa et al[29]
	Second line or more	145	13	NA	NA	NA	NA	NA	Hussein et al[30]
Phase III	Second line	272	20	3.5 (2.1–4.9)	NA	NA	9.2 (7.3–13.3)	42	Brahmer et al[31]
Pembrolizumab									
Phase I	Any line	95	26.3	6.1 (4.2–8.2)	NA	NA	14.9 (10.7 NR)	NA	Garon et al[45]
Atezolizumab (MPDL3280A)									
Phase I	Any line	11	27	NA	46	NA	NA	NA	Lynch et al[42]
Durvalumab (MEDI4736)									
Phase I	Any line	82	21	NA	NA	NA	NA	NA	Zielinski et al[43]

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

chemotherapy with or without an EGFR or ALK TKI. In the SCC group, the overall response rate (ORR) was 25.7%, with a disease control rate of 54.3% and PFS of 4.2 months. OS was not reached.[29] In the second study conducted primarily at community research sites (CHECKMATE 153, CA209-153), 824 patients with advanced or metastatic NSCLC, of which 227 patients (28%) were SCC histologic subtype, were treated for 1 year with nivolumab, after which they were randomized to nivolumab treatment until progression or discontinuation of nivolumab with rechallenge upon progression. In patients with squamous cell NSCLC, the ORR and stable disease at first assessment were 13% and 50%, respectively. No new safety signals were identified in this study. Interestingly, 8% of patients with NSCLC had a performance status of 2, and in these patients, the partial response rate was 20% with a disease control rate of 66%.[30]

Phase III studies

The promising results in SCC in particular led to the development of a Phase III study of nivolumab in advanced SCC (CHECKMATE 017).[31] In this study, 272 patients were randomized to nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks. The median age was 63 years, 76% were males, 80% had stage IV disease, 76% had ECOG performance status of 1, 6% had central nervous system metastasis, 92% were current or former smokers, and 45% completed their most recent treatment 3 months prior to study entry. With a minimum follow-up of 11 months, the primary end point of OS was reached with a median OS of 9.2 vs 6.0 months (HR 0.59, 95% CI 0.44–0.79, $P<0.001$) favoring nivolumab (Table 1). The HRs for OS favored nivolumab across all prespecified subgroups, except for the subgroups of patients in the rest-of-world geographic region (Argentina, Australia, Chile, Mexico, and Peru) and those ≥75 years of age. The use of nivolumab was associated with an improvement in 1-year OS rate (42% vs 24%) and PFS (3.5 vs 2.9 months; HR 0.62, 95% CI 0.47–0.81, $P<0.001$). In a recent update with a minimum follow-up of 18 months, the OS was 9.2 vs 6 months (HR 0.62, 95% CI 0.48–0.81, $P=0.0004$), and the PFS was 3.5 vs 2.8 months (HR 0.63, 95% CI 0.48–0.83, $P=0.0008$).[32] In patients receiving nivolumab, 21% were treated beyond RECIST 1.1 defined progression, and nonconventional benefit was reported in 7% of patients. The ORR and the median time to response in the nivolumab vs docetaxel cohorts were 20% vs 9% ($P=0.008$) and 2.2 vs 2.1 months, respectively. The survival benefits of nivolumab were independent of PD-L1 expression levels and were seen across all clinical subgroups. The role of biomarkers will be discussed in further detail subsequently.

Patient-related outcomes, as assessed with the Lung Cancer Symptom Scale (LCSS) in CHECKMATE 017, were recently presented. At week 12, 20.0% of patients treated with nivolumab and 21.9% of patients treated with docetaxel had clinically meaningful symptom improvement. Importantly, patients who remained on nivolumab showed greater symptom improvement and most symptoms showed significant improvement, while patients on docetaxel initially remained stable, subsequently had symptom deterioration. The time to first disease deterioration as measured by LCSS Global Health Related Quality of Life was longer in patients treated with nivolumab than in docetaxel patients (HR 0.58, 95% CI 0.39–0.86).[33] Patient-reported outcomes were also measured by EQ-5D and EQ-5D VAS scales, which showed improved scores in the nivolumab arm, with a HR of time to first disease-related deterioration on the EQ-5D index being 0.55 (95% CI 0.36–0.84).[34] While the results may be influenced by information bias as the study assessment times were different in the nivolumab and docetaxel arms, these results are significant as they are the first prospectively collected data to characterize the beneficial effect of immune checkpoint inhibitors using patient-related outcomes.

Based on the CHECKMATE 063 and CHECKMATE 017 studies, nivolumab has been approved by the FDA for the treatment of patients with metastatic SCC with progression on or after platinum-based chemotherapy.[35]

The benefits of nivolumab are not confined to SCC. CHECKMATE 057 compared nivolumab with docetaxel after platinum chemotherapy in patients with advanced-stage nonsquamous NSCLC. The OS was 12.2 vs 9.4 months (HR 0.73, 95% CI 0.59–0.89) favoring nivolumab, with improvements in 12- and 18-month survival rates (12-month OS 51% vs 29%, 18-month OS 39% vs 23%) and response rates (19% vs 12%, $P=0.02$), although no significant difference in PFS was observed.[36] This led to the approval of nivolumab by the FDA in October 2015 for the treatment of nonsquamous lung cancers.[37] PD-L1 expression was associated with benefit from nivolumab.

Clinical trials are currently underway to see if nivolumab may be a valid alternative to platinum doublet chemotherapy in the first-line setting. A Phase I trial of first-line nivolumab in NSCLC (both squamous and nonsquamous) has reported preliminary results of its first 20 patients, with an objective response rate of 30% (67% in PD-L1+ patients and 0% in PD-L1- patients, using a 5% threshold for PD-L1 expression) (NCT01454102).[38] Further work is required to define the ideal sequence of treatments and how to identify the patients most likely to benefit from immunotherapy.[39]

CHECKMATE 026, a first-line study of nivolumab compared with platinum doublet chemotherapy in PD-L1-positive patients, has completed accrual and the results, when available, may potentially change the landscape of first-line treatment of metastatic NSCLC.

Combinations

The efficacy of nivolumab as a single agent in NSCLC has been demonstrated. Studies are now underway to look at it in combination with various other modalities of treatment.

Dual immune-blockade of PD-1 and CTLA4 pathways has shown encouraging results in melanoma, and is now being tested in NSCLC. Combinations of the anti-CTLA4 antibody ipilimumab have been studied together with nivolumab or pembrolizumab in early phase studies, with promising response rates of 20%–55%.[40,41] Initially, the use of these combinations was limited by toxicities, with grade 3 and 4 toxicities affecting up to 50% of patients. However, the CHECKMATE 012 study evaluated several new dosing schedules for this combination, including nivolumab at 1 mg/kg every 2 weeks with ipilimumab at 1 mg/kg every 6 weeks, the same regimen with nivolumab 3 mg/kg every 2 weeks, and nivolumab at 3 mg/kg every 2 weeks with ipilimumab at 1 mg/kg every 12 weeks. These doses were well tolerated, with 3%–10% of patients discontinuing treatment due to adverse events. Grade 3 or 4 toxicities occurred in 28%–35% of patients but were generally manageable.[41]

Nivolumab has been combined with platinum-based doublet chemotherapy in the first-line treatment of NSCLC, with an overall response rate ranging from 33% to 47% depending on histology and chemotherapy regimen.[42]

Combination therapy involving other immune checkpoint inhibitors has also been studied. A three-arm Phase II study was conducted comparing concurrent ipilimumab and chemotherapy followed by chemotherapy (carboplatin and paclitaxel), phased chemotherapy followed by ipilimumab and chemotherapy combined, or chemotherapy with placebo. The phased schedule of ipilimumab with chemotherapy resulted in a prolonged PFS over chemotherapy alone: immune-related PFS 5.7 vs 4.6 months (HR 0.72, 95% CI 0.50–1.06). Interestingly, patients with SCC showed greater improvements in immune-related PFS (HR 0.55 vs 0.82) and OS (HR 0.48 vs 1.17) with the addition of ipilimumab compared to non-squamous histologies.[43,44]

Safety and tolerability

In the study of Japanese of single agent nivolumab in advanced-stage squamous and non-squamous cell NSCLC (ONO-4538-05), any grade drug-related adverse events were reported in 68.6% of squamous cell NSCLC patients. Decreased appetite, malaise, pyrexia, and rash were the commonest toxicities at 14.3% each. Grade 3–4 toxicities were reported in only 5.7%. The most frequent immune-related adverse event was skin toxicity, reported in 28.6% of patients. Other any grade immune-related toxicities included endocrine (11.4%), pulmonary (5.7%), gastrointestinal (5.7%), hepatic (5.7%), infusion reactions (5.7%), and renal (2.9%).[29] No grade 3–4 toxicities were seen.[29]

In the nivolumab monotherapy study CHECKMATE 063, any grade treatment-related adverse events were reported in 74% of patients and included fatigue (33%), decreased appetite (19%), nausea (15%), asthenia (12%), rash (11%), and diarrhea (10%). The incidence of grade 3–4 toxicities was 17%. The most frequent any grade treatment-related immune-mediated adverse events were skin disorders (15%) and gastrointestinal events (10%), endocrine (5%) and pulmonary (5%). Treatment-related adverse events led to discontinuation of the drug in 12% of patients.[28]

In the Phase III study of second-line nivolumab vs docetaxel (CHECKMATE 017), 58% of patients treated with nivolumab had any grade toxicities, while the rate of grade 3 or 4 toxicities was 7%, results consistent with previous nivolumab studies. In the docetaxel arm, 86% of patients had any grade events, and 55% had grade 3 or 4 toxicities. There were no treatment-related deaths in the nivolumab arm, whereas three deaths (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis) were reported in the docetaxel arm. The most frequently reported adverse events in patients treated with nivolumab were fatigue (16%), reduced appetite (11%), and asthenia (10%), while in the docetaxel arm, neutropenia (33%), fatigue (33%), alopecia (22%), and nausea (23%) were the most frequently reported adverse events. The most frequently reported (in ≥3% of patients) selected treatment-related adverse events observed with the use of nivolumab and docetaxel were hypothyroidism (4% vs 0%), diarrhea (8% vs 20%), pneumonitis (5% vs 0%), elevated blood creatinine (3% vs 2%), and skin rash (4% vs 6%). Discontinuation due to treatment-related adverse events was also higher in the docetaxel arm. A total of 10% of patients on docetaxel stopped treatment, with peripheral neuropathy being the most common cause, whereas only 3% stopped nivolumab, mainly due to pneumonitis.[31]

Longer term follow-up did not produce any unexpected adverse events with nivolumab maintaining a favorable safety profile compared with docetaxel.[32] The time to onset of

treatment-related select adverse events was 0.3–17.6 weeks in the nivolumab group, with the majority of patients experiencing their first treatment-related adverse event within the first 3 months of treatment.[31,32] Taken together, the safety profile of nivolumab in the CHECKMATE 017 study was consistent with prior studies and was favorable in comparison with docetaxel, with most patients having low-grade adverse events.

Biomarkers

One of the biggest challenges currently in studies of immune checkpoint inhibitors in NSCLC is to determine biomarkers that would identify patients most likely to respond to nivolumab. Multiple studies have examined the role of PD-L1 expression as a predictive marker for immune checkpoint therapy with conflicting results. In early phase studies, PD-L1 expression in tumor cells or tumor infiltrating lymphocytes or both was associated with response to PD-1/PD-L1 inhibitors.[20,45] However, responses are also seen in PD-L1-negative tumors.

In CHECKMATE 063, PD-L1 expression in pretreatment archival tumor samples was assessed in 74% of patients. The response rate in patients with tumor PD-L1 expression $<5\%$ and $\geq 5\%$ was 14% and 24%, respectively. Reductions in the target tumor lesion burden were seen in 52% of patients with PD-L1-positive tumors and in 38% of PD-L1-negative tumors.[28] These results should be interpreted with caution given the small sample size and the archival nature of the samples tested.

In CHECKMATE 017, PD-L1 expression was assessed by retrospectively evaluating pretreatment tumor biopsy specimens. This was done in 83% of the patient population. Across the prespecified expression levels (1%, 5%, and 10% cutoff), PD-L1 expression was neither prognostic nor predictive of OS or PFS.[31] Patients treated with nivolumab had similar OS and PFS to those in the primary population. The objective response rates observed among patients with PD-L1-positive tumors and those with PD-L1-negative tumors were similar. In the Checkmate 017 study, the response rate PD-L1 expression cutoff for $<1\%$ and $>1\%$ was 17% and 17%, respectively, $<5\%$ and $>5\%$ was 15% and 21%, respectively, and $<10\%$ and $>10\%$ was 16% and 19%, respectively.[31] In KEYNOTE-001, a cutoff of membranous PD-L1 in at least 50% of tumor cells was selected. The response rate of 45.2% in patients with PD-L1 $\geq 50\%$ was higher when compared to other groups, which had rates of 16.5% when the PD-L1 level was 1%–49% and 10.7% when the PD-L1 level was $<1\%$.[21] By contrast, in CHECKMATE 057, PD-L1-positive patients treated with nivolumab showed improved OS, PFS, and duration of response at the predefined 1%, 5%, and 10% cut points.[36] These observations may suggest inherent differences in the tumor microenvironment between squamous cell cancer vs non-squamous cancer, consistent with the notion that these are two distinct diseases.

As described earlier, PD-L1 expression may or may not be predictive of response, as patients with tumors considered to be PD-L1 negative also had responses to PD-1 inhibitors. This limitation in the predictive role of PD-L1 expression in various studies reflects the challenges of using PD-L1 as a predictive marker. In fact, several factors may affect the detection of tumor PD-L1 expression. First, there may be tumor heterogeneity, both within the tumor and between the primary and metastatic disease.[46–48] Second, PD-L1 expression across time may be dynamic and dependent on previous treatment.[49] As a result, PD-L1 staining on archival tumor tissues may not necessarily be representative of the tumor at the time of treatment. In CHECKMATE 017, archival or a recent biopsy sample was used for PD-L1 testing, whereas in CHECKMATE 063, archival samples were used. In addition, each of the different immune checkpoint inhibitors being developed has employed different methods to detect PD-L1 including different antibody clones, staining protocols/platforms, assessment within the tumor microenvironment (tumors cells, and/ or immune cells), and cutoffs to define positivity, further adding complexity to the interpretation of PD-L1 expression across different studies.[50]

To improve patient selection for immune checkpoint inhibition, other biomarkers have been explored. Increased nonsynonymous mutational load and neoantigen burden were associated with improved outcomes in patients with NSCLC and melanoma treated with pembrolizumab and ipilimumab, respectively.[51,52] In addition, the presence of mismatch repair gene deficiencies in tumors predicted for clinical benefit to pembrolizumab. Having an interferon gamma inflammatory gene signature was associated with PFS and OS benefits in melanoma patients treated with pembrolizumab, and CD8+ T-cell infiltration predicted for tumor regression in melanoma patients treated with pembrolizumab.[53–55]

The future

Immunotherapy has shown great promise in its role in NSCLC, with nivolumab as one of the frontrunners in terms of efficacy, particularly in SCC, where docetaxel may have lower efficacy compared to its role in non-SCC cancers. The positive results from CHECKMATE 017 study have established its role as a superior option for second-line therapy in SCC after progression on platinum doublet compared

to single-agent docetaxel treatment. Further studies of nivolumab in first-line setting are currently underway, and results are highly anticipated.

The appeal of immune checkpoint inhibitors is augmented by its tolerability, with toxicity profiles from various trials indicating better tolerance compared to standard chemotherapy treatment. While there are concerns with immune-related toxicities, these have been observed in <10% of patients in most trials, with grade 3–4 pneumonitis observed in ~2%–5% overall.

Nonetheless, unanswered questions remain in the landscape of immunotherapy, including that of optimal patient selection and its possible role in combination with other chemotherapy or immunotherapeutic agents.

As studies continue to evaluate the expression of PD-1 and PD-L1 on tumor and immune cells and their correlation to treatment response and outcomes, we may be able to better define and select patients who are most likely to respond to immune checkpoint inhibitors. The concept that PD-L1 expression may be modulated by previous therapies also highlights the importance of repeat tumor sampling in order to obtain accurate data to make informed choices for therapy for patients.

Conclusion

Nivolumab has shown proven benefit in the treatment of metastatic advanced-stage squamous NSCLC. It is currently approved by the FDA for the treatment of both squamous and non-squamous NSCLC. Several studies are underway to examine its role in first-line setting and also in combination with chemotherapy or other immunotherapeutic agents. An exciting new era awaits.

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