DRUGS IN CONTEXT
REAL-WORLD MEDICINE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

REVIEW

Metastatic squamous cell non-small-cell lung cancer (NSCLC): disrupting the drug treatment paradigm with immunotherapies

Sarah L Scarpace[1,2]

[1]Albany College of Pharmacy and Health Sciences, Albany, NY 12208, USA; [2]St. Peter's Health Partners Cancer Care Center, Albany, NY, USA

Abstract

Lung cancer is the third most commonly diagnosed cancer and the leading cause of cancer-related death in the United States. Unlike non-squamous NSCLC, squamous NSCLC rarely harbor epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations for which there are directed therapies, and until the recent approval of immunotherapies for squamous NSCLC, a limited number of traditional cytotoxic chemotherapy drugs have been FDA-approved for use in the treatment of advanced and metastatic squamous NSCLC. Immunotherapies directed at the programmed cell death-1 receptor (PD-1) or its ligand (PD-L1) (nivolumab and pembrolizumab) have demonstrated efficacy in both nonsquamous and squamous cell NSCLC. Because of their similar mechanism of action against the PD-L1/PD-1 pathway, both drugs have similar toxicity profiles related to immune-mediated adverse reactions that can generally be monitored and managed with oral corticosteroids. This paper provides an overview of drug therapy options for squamous cell NSCLC with a focus on the evidence and clinical application of the anti-PD1 therapies. A comparison of the dosing, administration, indications, and differences in the measurement of PD-L1 expression in the clinical trials of nivolumab and pembrolizumab is also provided.

Keywords: antibodies, carcinoma, squamous cell, non-small-cell lung cancer, immunotherapy, molecular targeted therapy, antibodies, monoclonal, nivolumab, pembrolizumab, cisplatin, carboplatin, gemcitabine, pemetrexed, ramucirumab, bevacizumab, programmed cell death-1 receptor, avelumab, MSB0010718C, MPDL3280A, MEDI4736.

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death-1 receptor; PD-L1, programmed cell death-1 receptor ligand.

Citation

Scarpace SL. Metastatic squamous cell non-small-cell lung cancer (NSCLC): disrupting the drug treatment paradigm with immunotherapies. Drugs in Context 2015; 4: 212289. DOI: 10.7573/dic.212289

Introduction

Lung cancer is the third-most commonly diagnosed cancer and the leading cause of cancer-related deaths in the United States [1]. Over 220,000 new cases of lung cancer are expected to be diagnosed in 2015 while more than 158,000 people are expected to die from lung cancer that same year [1]. Worldwide, lung cancer is the leading cause of both new cancer diagnoses and cancer-related deaths with nearly 1.8 million new cases and 1.6 million deaths estimated in 2012 (the most recent year for which data is available) [2]. Most (approximately 85%) of lung cancers are of the non-small-cell type (NSCLC), with 25–30% of NSCLC being squamous histology type [3]. Unlike nonsquamous NSCLC, squamous NSCLC rarely harbors epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations for which there are directed therapies [4], and until the recent approval of immunotherapies for squamous NSCLC, a limited number of traditional cytotoxic chemotherapy drugs have been FDA-approved for use in the treatment of advanced and metastatic squamous NSCLC.

The programmed cell death-1 receptor (PD-1) is found on cytotoxic T cells and T-regulatory cells and is expressed when T cells become activated in response to inflammation or infection in peripheral tissues [5,6]. Binding of the PD-1 ligand to its receptor inactivates the T cell in order to limit the immune response to the stimuli, thus causing an immune suppression [5,6]. Cancer cells induce PD-1 expression, enhancing the immunosuppressive action of this pathway, ultimately allowing the cancer to be "hidden" from natural immune attack [5,6]. Anti-PD-1 therapies disrupt this pathway by preventing the PD-1 ligand from binding to its receptor, leaving activated

cytotoxic T cells available to attack the cancer cells [5,6]. Immunotherapies directed at the PD-1 or its ligand (PD-L1) have demonstrated efficacy in both nonsquamous and squamous cell NSCLC [7,8]. Notably, while EGFR, Kirsten rat sarcoma viral oncogene homolog (KRAS), and ALK mutation status guide drug therapy selection and provide more treatment options for patients who harbor these mutations (typically nonsquamous NSCLC), patients with squamous cell disease with larger tumors or positive lymph nodes who express PD-L1 may have improved survival compared with their PD-L1-deficient counterparts [9]. It is not known, however, what minimum level of PD-L1 expression is necessary to predict treatment outcomes with anti-PD-1 therapies because while patients who are PD-L1 positive have higher response rates to treatments across various tumor types, it has been shown that even patients who test negative for PD-1 can respond to these therapies [10].

Drug therapy overview

A platinum-based combination chemotherapy regimen has been the standard first-line treatment for all NSCLC since cisplatin was first FDA-approved in 1978 [11]. Carboplatin is frequently substituted for cisplatin for patients who have poor renal function or who experience toxicities from cisplatin (most notably, nausea and vomiting) [12]. Taxanes, especially paclitaxel in the first-line setting or docetaxel in refractory patients, commonly complete the standard two-drug backbone of platinum-based chemotherapy for the first-line treatment of NSCLC. In combination, platinum with a taxane frequently causes myelosuppression, nausea, vomiting, alopecia, paronychia, stomatitis, fatigue, taste changes, and, particularly when docetaxel is used as part of the regimen, febrile neutropenia and subsequent risk of systemic infections [13,14]. Gemcitabine, etoposide, vincristine, vinorelbine, and pemetrexed have also been evaluated in combination with a platinum agent in the first line-setting for NSCLC [15,16]. Of note, patients with nonsquamous cell disease have improved survival with cisplatin and pemetrexed combination therapy in the first-line setting compared with combination cisplatin and gemcitabine, whereas patients with squamous cell disease have improved survival with cisplatin and gemcitabine combination treatment [16]. While cisplatin and pemetrexed have demonstrated higher rates of severe nausea compared with cisplatin and gemcitabine, patients treated with cisplatin and gemcitabine experienced higher rates of severe neutropenia, anemia, thrombocytopenia, febrile neutropenia, and alopecia [16].

For patients with squamous cell NSCLC, several traditional cytotoxic chemotherapy options are available for subsequent treatment, including single-agent docetaxel or gemcitabine (if not used in the first-line setting) or combination gemcitabine with the vascular endothelial growth factor receptor monoclonal antibody ramucirumab [17]. The rare squamous cell NSCLC patient with wild-type EGFR status may be offered erlotinib or gefitinib if not used first-line [18]. Both docetaxel–ramucirumab and single-agent nivolumab have shown improved survival for squamous cell NSCLC patients in the second-line setting compared with single-agent docetaxel; however, nivolumab has been given a category 1 recommendation by the National Comprehensive Network's clinical practice guideline for non-small-cell lung cancer for the second-line treatment of squamous cell disease after failure of first-line platinum-based treatment.

Because of their novel mechanism of action and because the traditional cytotoxic agents have been available for so long with known efficacy and toxicities, the remainder of this review will focus on the clinical trial experience of the anti-PD-1 therapies nivolumab and pembrolizumab, currently the only immunotherapies that are FDA-approved for the treatment of NSCLC. These therapies represent a novel approach to treating NSCLC and spare the patient from the myelosuppresive and emetic effects of the traditional cytotoxic chemotherapy described above. Nivolumab is currently FDA-approved only for squamous cell NSCLC; most recently, pembrolizumab received FDA-approval for any histological type of NSCLC as long as the tumor tests positive for PD-1 expression. In contrast, nivolumab was not approved with the condition that the tumor test positive for PD-1 expression.

Anti-PD-L1 immunotherapy for squamous NSCLC

When the PD-1 ligand binds to its receptor on activated T cells, the T cell is unable to exert its immunologic effects on antigens, including cancer cells [5,6]. Many cancer cells, including those of NSCLC, express the PD-1 ligand, and the ligand–receptor binding essentially allows the cancer to "hide" from the T cell. Current smokers are significantly more likely to express the PD-1 receptor than nonsmokers [19]. In fact, current/former smokers with NSCLC were significantly more likely to respond to anti-PD-1 therapy with pembrolizumab than never-smokers; however, once corrected for PD-1 expression of at least 50%, smoking status was not as robust of a predictor of response to treatment [9]. Current/former smokers with squamous NSCLC were also significantly more likely to respond to nivolumab than docetaxel compared with never-smokers; in this trial, PD-1 expression did not predict response to treatment (though the maximum expression level measured was 10%) [8]. Drugs that block the binding of the PD-1 ligand to its PD-1 receptor, such as nivolumab and pembrolizumab, allow activated T cells to identify and attack cancer cells. In clinical trials that have evaluated nivolumab and pembrolizumab activity against various cancers, including NSCLC, an apparent pseudoprogression of the cancer has been noted because of the infiltration of the T cells into the site of the primary tumor, which on imaging makes the mass appear to have increased in size [5,9]. It may take up to 6 months to have a clear picture of a patient's true response to treatment because of this T-cell infiltration, and some have called for an alternative to the Response Evaluation Criteria

in Solid Tumors (RECIST) criteria and other parameters for monitoring and measuring response to treatment because of this phenomenon [5,6,9].

CheckMate 063 was a phase 2, single-arm trial conducted in Europe and the United States of nivolumab 3 mg/kg IV over 1 hour every 2 weeks until disease progression or unacceptable toxicity in 117 patients with stage IIIB or IV squamous cell NSCLC that had progressed on at least two prior treatment regimens—a platinum-doublet therapy and one additional drug therapy regimen (one-third of patients were previously treated with an anti-EGFR tyrosine kinase inhibitor) [8]. In fact, two-thirds of patients had progressed following three systemic regimens. Patients who had apparent disease progression on radiographic images were allowed to continue treatment at the discretion of their physician if it was determined that the patient was experiencing a clinical benefit because of the known pseudo-progression that can occur with anti-PD-1 therapy. Patients with stable brain metastases were eligible for enrollment in the trial, which is notable because such patients are frequently excluded from clinical trials, particularly when they have squamous histology, because of the tendency for this histology to bleed. In this trial, two patients (2%) had brain metastases. Other interesting eligibility criteria for this trial include that while patients with interstitial pneumonitis were excluded, patients with a history of pneumonitis were not; of note, pneumonitis was one of the three most common National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC) grade 3–4 adverse events reported in the trial. Another notable detail regarding the study procedures was that dose modifications were not allowed, although criteria were established for dose delays. This is an important aspect of the protocol for clinicians to be aware because dose modifications in clinical oncology practice are frequent and sometimes empiric. PD-L1 status was assessed on pretreatment, formalin-fixed, and paraffin-embedded tumor specimens and was considered positive if 5% of the cells stained positive by a validated immunohistochemical (IHC) assay. As noted earlier, the relevance and exact lower threshold for meaningful PD-L1 positivity is an area of clinical controversy, and the KEYNOTE trial of pembrolizumab used a much higher breakpoint (50%) for PD-L1 expression [9–11].

A median of six doses of nivolumab were administered to patients in CheckMate 063 with a median treatment duration of 2.3 months (95% CI, 1.4–2.8 months). 14.5% of patients achieved a partial response by RECIST and 26% had stable disease. The most common reason for treatment discontinuation was disease progression (67% of patients). Patients were assessed by radiographic imaging at baseline, 8 weeks after the start of treatment, and then every 6 weeks until disease progression. On this imaging schedule, median time to response was reported as 3.3 months and median duration of response had not been reached (minimum follow-up for response was 11 months and median follow-up for overall survival was 8 months). The median duration of stable disease was 6 months. Although survival was a secondary end point in this phase 2 trial, the reported median progression-free survival was 1.9 months (95% CI, 1.8–3.2 months) and median overall survival was 8.2 months (95% CI, 6.1–10.9 months). Patients with greater than or less than the 5% threshold for PD-L1 positivity responded to treatment, although those with at least 5% positivity had numerically higher rates of partial response (24 *vs* 14%) and lower rates of progressive disease (44 *vs* 49%) compared with those with less than 5% PD-L1 positivity.

The most common adverse events of any NCI CTC grade reported in CheckMate 063 were fatigue (33%), decreased appetite (19%), nausea (15%), asthenia (12%), rash (11%), and diarrhea (10%); the most common severe (NCI CTC grade 3 or 4) adverse events reported were fatigue (4%), pneumonitis (3%), and diarrhea (3%). Immune-related toxicities were anticipated in the trial because of the mechanism of action of the drug; however, most were of low grade with most being skin or gastrointestinal in nature. High-dose oral corticosteroids are the general management strategy for the immune-related adverse events. Given the activity of nivolumab in this phase 2 trial with tolerable/manageable toxicities, nivolumab was a candidate for more rigorous evaluation in a phase 3 trial.

The same dose and schedule of nivolumab was further evaluated in comparison with standard docetaxel 75 mg/m^2 IV every 3 weeks in CheckPoint 017, a phase 3, randomized, open-label, international study of 272 patients with stage IIIB or IV squamous cell NSCLC who failed only one prior platinum-containing treatment [5]. Similar to the phase 2 CheckPoint 063, patients with treated, stable brain metastases were eligible for enrollment, and dose reductions in nivolumab were not allowed. A total of 6% of patients in the trial had CNS metastasis (7% of nivolumab patients and 6% of docetaxel patients). Unlike CheckPoint 063, however, no nivolumab patients and only 1% of docetaxel patients had been treated with anti-EGFR therapy (only cetuximab use was reported for CheckPoint 017, whereas the oral tyrosine kinase inhibitors against EGFR were reported for CheckPoint 063). The most common first-line chemotherapies used with a platinum in CheckPoint 017 were gemcitabine (48%), paclitaxel (34%), and vinorelbine (16%). CheckPoint 017 was initially designed around the primary end point of response rate; however, the protocol was amended after interim results were reported from the MDX-1106-03 trial to make overall survival the primary end point. The study was stopped early because a prespecified interim analysis showed that overall survival was significantly improved on the nivolumab arm compared with the docetaxel arm. At the time that the study closed, enrollment numbers had already been met. At the data cutoff, median overall survival was 9.2 months (95% CI, 7.3–13.3 months) on nivolumab compared with 6.0 months (95% CI, 5.1–7.3 months) on docetaxel, with a 41% reduction in the risk of death on the nivolumab arm (HR, 0.59; 95% CI, 0.44–0.49; $p<0.001$). Objective response was also significantly higher on the nivolumab arm compared with docetaxel (20% [95% CI, 14–28%] *vs* 9% [95% CI, 5–15%]; $p=0.008$), and it took approximately 2 months on both arms to observe a response (patients were monitored with radiographic

imaging at baseline, week 9, and every 6 weeks thereafter). Statistically, the median progression-free survival was not different between the arms with 3.5 months (95% CI, 2.1–4.9 months) on nivolumab compared with 2.8 months (95% CI, 2.1–3.5 months) on docetaxel, although the cumulative risk of progressive disease over the course of the trial was significantly improved with nivolumab with a 38% reduction in the risk of progression (HR, 0.62; 95% CI, 0.47–0.81; $p<0.001$). In this trial, no level of PD-L1 positivity by IHC staining (1, 5, and 10% levels were evaluated) predicted response or was prognostic for survival. Nivolumab was better tolerated than docetaxel. 85% of nivolumab patients received at least 90% of their planned dose intensity, compared with only 69% of docetaxel patients. Patients were also more likely to discontinue treatment due to adverse events of docetaxel (10% of patients) than of nivolumab (3% of patients). Furthermore, 58% of patients on nivolumab experienced any NCI CTC grade of adverse event compared with 86% of docetaxel patients, 7% of which were grade 3 or 4 on nivolumab compared with 55% on docetaxel. The most common adverse events on the nivolumab arm were fatigue (16%), decreased appetite (11%), and asthenia (10%), similar to what was seen in CheckPoint 063. Fatigue, decreased appetite, and leukopenia were the only grade 3 or 4 adverse events reported on nivolumab, each occurring in only 1% of nivolumab-treated patients.

Pembrolizumab is another anti-PD-L1, monoclonal antibody that, like nivolumab, is approved for refractory metastatic melanoma patients and recently received accelerated FDA-approval for the treatment of any histological type of NSCLC after failure of first-line therapy that includes a platinum or an anti-EGFR or anti-ALK therapy in patients with appropriate mutations. It has been evaluated in the phase 1 KEYNOTE-001 trial at doses of 2 or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks (in all cases administered as a 30-minute infusion) in 495 patients who were either treatment-naive or treatment-experienced with any histologic type of stage IIIB or IV NSCLC to determine the preliminary safety and efficacy of pembrolizumab in this population [9]. Patients were monitored for response by traditional radiographic imaging and RECIST criteria every 9 weeks as well as investigator-assessed, immune-related response criteria. Biopsy samples had to be available for enrollment, and in the biomarker validation component of the trial, those samples with at least 1% of cells expressing PD-L1 by IHC staining were considered PD-L1 positive. The overall response rate was 19.4% (95% CI, 16.0–23.2%). Previously untreated patient were more likely to respond to therapy (24.8; 95% CI, 16.7–34.3%) and to have longer median duration of response (23.3 months; 95% CI, 1.0–23.3 months) than those patients who were treatment-experienced (18.0% response rate; 95% CI, 14.4–22.2%; median duration of response 10.4 months; 95% CI, 1.0–10.4 months). There were no differences in the response rate based on histologic subtype (squamous *vs* nonsquamous) or based on the dose or schedule of pembrolizumab. Current/former smokers had higher response rates (22.5%) compared with never-smokers (10.3%).

Median overall survival reported in this phase 1 trial was also longer for patients receiving pembrolizumab as first-line therapy (16.2 months; 95% CI, 16.2–not reached) compared with those receiving pembrolizumab after failing at least one prior regimen (9.3 months; 95% CI, 9.3–14.7 months). The KEYNOTE-001 investigators selected 50% PD-L1 expression as the cutoff for PD-L1 positivity, which was found in almost one-quarter of the population; at this level, the overall response rate was 45.2% (95% CI, 33.5–57.3%), and differences in response between previously treated and previously untreated patients were no longer apparent (43.9% response rate [95% CI, 30.7–57.6%] in previously treated patients compared with 50.0% response rate [95% CI, 24.7–75.3%] in previously untreated patients). Side effects that were seen with pembrolizumab were of similar nature as those seen with nivolumab, although some seem numerically higher than that reported in the nivolumab trial. More grade 3–5 dyspnea (3.8%) and pneumonitis (1.8%) and more overall pruritis (10.7%), rash (9.7%), arthralgia (9.1%), diarrhea (8.1%), and nausea (7.5%) were reported with pembrolizumab in this phase 1 trial. Additionally, 6.9% of patients experienced any grade of hypothyroidism (only 1 patient (0.2%) experienced grade 3–5 hypothyroidsim). The most common adverse events of any severity in KEYNOTE-001 were fatigue, pruritus, decreased appetite, rash, arthralgia, diarrhea, nausea, and hypothyroidism (all occurring in more than 5% of patients) and the most common grade 3–5 adverse events were dyspnea (3.8%), pneumonitis (1.8%), decreased appetite (1%), and asthenia (1%).

Treatment selection: nivolumab compared with pembrolizumab

Both nivolumab and pembrolizumab offer an important drug therapy option for selected patients in the second-line treatment of NSCLC. Pembrolizumab received accelerated FDA-approval based on the outcomes of a phase 1 trial and is awaiting confirmatory results from phase 3 trials to establish its effects on overall and progression-free survival. In contrast, nivolumab received standard FDA-approval based on the outcomes of a phase 3 trial demonstrating improved survival in comparison with docetaxel, an accepted second-line therapy for patients who fail platinum-doublet therapy. Because of their similar mechanism of action against the PD-L1/PD-1 pathway, both drugs have similar toxicity profiles related to immune-mediated adverse reactions that can generally be monitored and managed with oral corticosteroids. Pembrolizumab requires less frequent administration at a dose of 2 mg/kg IV over 30 minutes every 3 weeks, compared with nivolumab 3 mg/kg IV over 60 minutes every 2 weeks. While nivolumab received FDA-approval strictly for squamous cell NSCLC, clinical trials demonstrated that both squamous and nonsquamous histologies respond to both nivolumab and pembrolizumab. Finally, pembrolizumab was approved for patients who test positive for PD-L1 (defined in the KEYNOTE-001 trial as at least 50%) based on differences in response rates for patients

who meet this threshold compared with those who fall below it; nivolumab was not approved with a PD-L1 expression contingency, though the CheckMate 063 trial only used 5% and the CheckMate 017 trial only used 10% PD-L1 threshold for determining response (and subsequently determined that PD-L1 expression using these definitions did not predict response). While smokers seem to be more likely to express PD-L1 and to respond to anti-PD-L1 therapies, using the 50% threshold for PD-L1 positivity more accurately predicts response to these therapies and therefore smoking status should not be used to select patients for treatment. Neither drug requires dose adjustment for renal or hepatic impairment unless immune-mediated nephritis or hepatitis occurs after the start of treatment. The decision of which anti-PD-L1 therapy to use in the second-line setting will generally depend currently on the histology of the patient, possibly PD-L1 expression, and the preference of the treating clinician to select therapy based on the efficacy reports from Phase 3 compared with Phase 1 trials. In most cases, second-line therapy options that do not include anti-PD-L1 therapy are cytotoxic chemotherapy; patients who may be unlikely to tolerate the typical adverse effects of these other traditional agents may be best suited for second-line anti-PD-L1 therapy.

Future directions

Anti-PD-L1/PD-1 therapies are the first immunotherapies to demonstrate clinical benefit in NSCLC. These are particularly important in the NSCLC population with squamous histology as the treatment options for these patients have been generally limited to traditional cytotoxic chemotherapies because of the infrequent presence of biomarker expression for which there are targeted therapies. For all NSCLC, validation of PD-L1 or PD-1 assays and a defined level of PD-L1/PD-1 expression to predict those most likely to benefit from treatment will be an important area of ongoing research. Published trials of nivolumab have evaluated its use in refractory patients, and it is currently unknown if there is clinical benefit to using this therapy in the first-line setting for all or a subset of NSCLC patients. KEYNOTE-001 included treatment-naive patients in the evaluation of pembrolizumab for NSCLC. CheckMate 026 (NCI clinical trial number NCT02041533) and KEYNOTE-042 (NCI clinical trial number NCT02220894) are phase 3 trials that are currently recruiting patients for the first-line treatment of NSCLC with nivolumab compared with investigator's choice chemotherapy (CheckMate 026) or pembrolizumab compared with platinum-based chemotherapy (KEYNOTE-042) in PD-L1-positive NSCLC with results expected in August 2016 (CheckMate 026) and June 2018 (KEYNOTE-042) [19,20]. KEYNOTE-024 (NCI clinical trial number NCT02142738) is also recruiting treatment-naive patients with strongly positive PD-L1-positive NSCLC in a phase 3 trial of pembrolizumab compared with platinum-based chemotherapy [21].

An additional area of clinical interest is the use of the anti-PD-1 therapies in combination with currently available treatments. The currently published trials of nivolumab and pembrolizumab have evaluated their use as single agents; trials are currently ongoing to evaluate these therapies in combination with other therapies, including chemotherapy, the anti-CTLA4 immunotherapy ipilimumab, and anti-EGFR targeted agents. CheckMate 227 (NCI clinical trial number NCT02477826) opened in August 2015 and is currently recruiting patients to evaluate nivolumumab with or without ipilimumab compared with standard platinum-doublet therapies in the first-line treatment of advanced or metastatic NSCLC for any histology, with preliminary results expected in May 2017 [22]. KEYNOTE-021 (NCI clinical trial number NCT02039674) is currently recruiting patients to a randomized, open-label, multiarm safety/efficacy study of pembrolizumab in combination with standard therapies with a control arm of standard platinum-doublet chemotherapy [23]. Additional trials are also ongoing with other anti-PDL1 therapies, including avelumab (MSB0010718C), MPDL3280A, and MEDI4736 [25].

Summary

Standard platinum-doublet therapy remains the primary drug therapy approach to treating patients with advanced/metastatic squamous cell NSCLC. Recent advances in anti-PDL1 immunotherapy have expanded the treatment armamentarium for this population of patients in the second-line setting. Phase 1–3 trials have demonstrated improved response rates and survival outcomes with acceptable levels of toxicity when nivolumab or pembrolizumab is used as monotherapy in this setting. There is a need for further research to better define the role of PD-L1 expression as a biomarker predictive of response to these treatments as well as how these treatments may be used in the first-line setting and/or in combination with existing standard therapies. Ongoing clinical trials evaluating these questions will help aid the clinician in determining the optimal approach to the medical management of advanced/metastatic squamous NSCLC.

Potential conflicts of interests: The International Committee of Medical Journal Editors' (ICMJE) Potential Conflicts of Interests form for the author is available for download at: http://www.drugsincontext.com/wp-content/uploads/2015/10/dic.212289-COI.pdf. The author has no relationships to disclose.

Funding declaration and acknowledgment: The author has declared that this is an unfunded review.

Article URL: http://www.drugsincontext.com/metastatic-squamous-cell-non-small-cell-lung-cancer-nsclc-disrupting-the-drug-treatment-paradigm-with-immunotherapies

Correspondence: Sarah L Scarpace, Albany College of Pharmacy and Health Sciences, Albany, NY 12208, USA; St. Peter's Health Partners Cancer Care Center, Albany, NY, USA. sarah.scarpace@acphs.edu

Provenance: Submitted, externally peer reviewed

Submitted: 15 September 2015; **Peer review comments to author**: 28 September 2015; **Publication date**: 14 October 2015

Drugs in Context is published by Just Medical Media Ltd. Registered office: Undermount, Rydal, Ambleside, Cumbria, LA22 9LT, UK

Just Medical Media Limited is registered in England Number 6891187. VAT GB 945 1713 22

For all manuscript and submissions enquiries, contact Julia Savory, Head of Digital Publishing and Submissions Management julia@justmedicalmedia.com

For all permissions, rights, and reprints, contact Stephen I'Anson, Commercial Director steve@justmedicalmedia.com

References

1. National Cancer Institute. SEER stat fact sheets: lung and bronchus cancer [cited 2015 Sep 12]. Available from: http://seer.cancer.gov/statfacts/html/lungb.html
2. World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality, and prevalence worldwide in 2012. Lung Cancer [cited 2015 Sep 12]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
3. American Cancer Society. Lung Cancer (Non-Small Cell) [cited 2015 Sep 12]. Available from: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer
4. Rekhtman N, Paik PK, Arcila ME, et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. Clin Cancer Res. 2012;18(4):1167–76. http://dx.doi.org/10.1158/1078-0432.CCR-11-2109
5. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Rev Cancer. 2012;12:252–64. http://dx.doi.org/10.1038/nrc3239
6. Tumeh PH, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568–71. http://dx.doi.org/10.1038/nature13954
7. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123–35. http://dx.doi.org/10.1056/NEJMoa1504627
8. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015;16:257–65. http://dx.doi.org/10.1016/S1470-2045(15)70054-9
9. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018–28. http://dx.doi.org/10.1056/NEJMoa1501824
10. Henning Schmidt L, Kummel A, Gorlich D, et al. PD-1 and PD-L1 expression in NSCLC indicate a favorable prognosis in defined subgroups. PLoS One. 2015;10(8):e0136023. http://dx.doi.org/10.1371/journal.pone.0136023
11. Carbognin L, Pilotto S, Milella M, et al. Differential activity of nivolumab, pembrolizumab and MPDL3280A according to the tumor expression of programmed death-ligand-1 (PD-L1): sensitivity analysis of trials in melanoma, lung, and genitourinary cancers. PLoS One. 2015;10(6):e0130142. http://dx.doi.org/10.1371/journal.pone.0130142
12. Food and Drug Administration. Drugs@FDA: Platinol. Label and approval history [cited 2015 Sep 13]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist
13. de Castria TB, da Silva EM, Gois AF, Riera R. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer. Cochrane Database Syst Rev. 2013;8:CD009256. http://dx.doi.org/10.1002/14651858.CD009256.pub2
14. Fossella F, Pereira JF, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003;21(16):3016–24. http://dx.doi.org/10.1200/JCO.2003.12.046
15. Belani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol. 2005;16:1069–75. http://dx.doi.org/10.1093/annonc/mdi216

16. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543–51.
17. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicenter, double-blind, randomised phase 3 trial. Lancet. 2014;384:665–73. http://dx.doi.org/10.1016/S0140-6736(14)60845-X
18. National Comprehensive Network. Clinical Practice Guidelines in Oncology: Non-small cell Lung Cancer. V.7.2015 [cited 2015 Sep 13]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nscl
19. D'Incecco A, Andreozzi M, Ludovini V, et al. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. Br J Cancer. 2015;112:95–102.
20. National Institutes of Health. Clinicaltrials.gov. NCI clinical trial number: NCT02041533 [cited 2015 Sep 15]. Available from: https://clinicaltrials.gov/show/NCT02041533
21. National Institutes of Health. Clinicaltrials.gov. NCI clinical trial number: NCT02220894 [cited 2015 Sep 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT02220894?term=pembrolizumab+and+lung&rank=9
22. National Institutes of Health. Clinicaltrials.gov. NCI clinical trial number: NCT02142738 [cited 2015 Sep 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT02142738?term=pembrolizumab+and+lung&rank=10
23. National Institutes of Health. Clinicaltrials.gov. NCI clinical trial number: NCT02477826 [cited 2015 Sep 15]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02477826?term=nivolumab+and+lung&rank=4
24. National Institutes of Health. Clinicaltrials.gov. NCI clinical trial number NCT02039674 [cited 2015 Sep 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT02039674?term=pembrolizumab+and+lung&rank=13
25. National Institutes of Health. Clinicaltrials.gov [cited 2015 Sep 15]. Available from: https://clinicaltrials.gov/ct2/results?term=PD-L1+and+lung&Search=Search