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REVIEW ARTICLE

Current landscape of immunotherapy for the treatment of metastatic non-small-cell lung cancer

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ABSTRACT

For patients with advanced non-small-cell lung cancer (NSCLC) lacking a targetable molecular driver, the mainstay of treatment has been cytotoxic chemotherapy. The survival benefit of chemotherapy in this setting is modest and comes with the potential for significant toxicity. The introduction of immunotherapeutic agents targeting the programmed cell death 1 protein (PD-1) and the programmed cell death ligand 1 (PD-L1) has drastically changed the treatment paradigms for these patients. Three agents—atezolizumab, nivolumab, and pembrolizumab—have been shown to be superior to chemotherapy in the second-line setting. For patients with tumours strongly expressing PD-L1, pembrolizumab has been associated with improved outcomes in the first-line setting.

Demonstration of the significant benefits of immunotherapy in NSCLC has focused attention on new questions. Combination checkpoint regimens, with acceptable toxicity and potentially enhanced efficacy, have been developed, as have combinations of immunotherapy with chemotherapy. In this review, we focus on the published trials that have changed the treatment landscape in advanced NSCLC and on the ongoing clinical trials that offer hope to further improve outcomes for patients with advanced NSCLC.

Key Words Non-small-cell lung cancer, immunotherapy, clinical trials

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BACKGROUND

Lung cancer is prevalent globally, with more than 1.6 million new cases being diagnosed annually, and it is a leading cause of cancer mortality, at 1.3 million deaths each year[1]. Most patients are diagnosed with non-small-cell lung cancer (NSCLC), comprising nonsquamous (70%) and squamous (30%) histologic subtypes[2]. Approximately 50% of all patients present with incurable metastatic disease which carries with it a dismal prognosis[3].

Immune checkpoint inhibitors have dramatically altered the landscape of therapy in melanoma, and the effectiveness of those agents has subsequently been studied in the treatment of myriad cancers, including NSCLC[4–6]. Immunotherapies targeting the programmed cell death 1 protein (PD-1)–programmed cell death ligand 1 (PD-L1) axis have demonstrated significant activity in NSCLC, and results from randomized trials have led to a rapid shift in the treatment paradigms in advanced NSCLC.

Many anti–PD-1 and –PD-L1 agents are in development. The focus of the present review is the agents that are furthest along in development and, in particular, the randomized trials that have contributed to changing the landscape in the management of advanced NSCLC.

EARLY EVIDENCE OF ACTIVITY: PHASE I SAFETY AND PHASE II TRIALS

One of the first phase I trials of PD-1 inhibition to be completed, CheckMate 003, used nivolumab (BMS-936558), a fully human immunoglobulin G4 monoclonal antibody that selectively inhibits the PD-1 receptor[6]. The study enrolled patients having several types of solid tumours, including metastatic NSCLC. Patients (n = 122) received nivolumab at a dose of 1–10 mg/kg once every 2 weeks for up to 12 cycles. The adverse events (AEs) most commonly observed were fatigue, diarrhea (11%), and rash (12%). Grades 3 and 4 toxicities were seen in 14% of patients. Immune-mediated events were infrequent, but included pneumonitis (3%), hypothyroidism (2%), and infusion reactions (3%). An objective response rate (ORR) of 17%, with durable responses, was observed in this heavily pretreated

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population. Durable responses represent those achieved by patients at the tail end of the survival curves, who are thought to benefit from longer responses, defined in the literature as having an objective complete or partial response by modified World Health Organization criteria beginning within 12 months of starting the study treatment and lasting at least 6 months from the time of onset[7].

Results of the NSCLC expansion cohort after longer follow-up were subsequently reported by Gettinger and colleagues[8]. Nivolumab was given to 129 patients, 54% of whom had received at least 3 prior lines of therapy, every 2 weeks for up to 96 weeks. In patients receiving the 3 mg/kg dose, the ORR was 24%, with a median duration of response of 17 months. An exploratory analysis suggested no association between PD-L1 expression and response.

CheckMate 063 was an international open-label single-arm phase II trial assessing the therapeutic activity of nivolumab for patients with advanced (stages IIIB and IV), squamous cell carcinoma who had received 2 or more prior lines of therapy[9]. Patients enrolled in the trial ($n = 117$) received nivolumab at a dose of 3 mg/kg every 2 weeks until progression or unacceptable toxicity, although treatment beyond progression was permitted in the protocol. The ORR was 14.5%, and the median duration of response was not reached at the time of reporting. Responses were seen in patients with both PD-L1–positive and –negative tumours. Grade 3 or 4 toxicities were seen in 17%, most commonly fatigue, pneumonitis, and diarrhea.

Pembrolizumab, another humanized immunoglobulin G4 monoclonal antibody against the PD-1 receptor, showed significant activity in the phase I KEYNOTE 001 trial[10]. Patients received pembrolizumab at a dose of either 2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks ($n = 495$). The most frequent AEs were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%), with no clear difference based on dose or schedule. Grade 3 or 4 toxicities occurred in 9.5% of patients. Immune-mediated events were again infrequent, but included pneumonitis (3.6%), hypothyroidism (6.9%), and infusion reactions (3%). The ORR was 19.4% in the patients overall, with no difference in efficacy based on dose or schedule. The responses were also found to be durable, with 84.4% of responders showing no disease progression at the time of reporting (median duration of response: 12.5 months). The KEYNOTE 001 trial also sought to validate PD-L1 expression as a predictive biomarker for pembrolizumab activity. Expression of PD-L1 was assessed by prototype immunohistochemistry assay using the 22C3 antibody. Membrane staining for PD-L1 on at least 50% of tumour cells (50% staining) was selected as the cut-off for the remainder of the trial and was validated in an independent cohort of patients. Staining of 50% or greater was associated with a higher ORR (45%) and greater overall survival [OS (median: not reached)].

Atezolizumab is a humanized anti–PD-L1 antibody that has also been associated with durable responses in patients with pretreated NSCLC[11]. Response was associated with PD-L1 expression on tumour cells and infiltrating immune cells. In the phase II BIRCH trial, an ORR of 17% was reported for cohorts of previously treated NSCLC patients selected for higher PD-L1 expression (two thirds of tumour cells or immune cells)[12].

PHASE III TRIALS IN PREVIOUSLY TREATED PATIENTS

In comparing the results of the randomized phase III trials in previously treated NSCLC, it is important to recognize the differences in trial design used for the three agents studied (Table I).

In the international open-label 1:1–randomized phase III CheckMate 017 trial, nivolumab was compared with docetaxel in the second-line setting in patients with advanced squamous cell lung cancer after platinum-doublet chemotherapy[13]. Patients received either nivolumab 3 mg/kg every 2 weeks ($n = 135$) or docetaxel 75 mg/m^2 every 3 weeks ($n = 137$) until progressive disease or toxicity. Treatment beyond radiographic progression was permitted if the patients were felt to be deriving clinical benefit. The primary endpoint was OS. The trial was stopped early, having met its target at a pre-specified interim analysis as assessed by an independent data and safety monitoring committee. Compared with docetaxel, nivolumab showed a significant OS benefit [9.2 months vs. 6.0 months; hazard ratio (HR): 0.59; 95% confidence interval (CI): 0.44 to 0.79; $p < 0.001$]. The ORR was 20% in the nivolumab arm; it was 9% for docetaxel. The median duration of response was not reached in the nivolumab group; it was 8.4 months in the docetaxel arm. Expression of PD-L1 stratified at 1%, 5%, or 10% was not found to be predictive or prognostic of benefit. Treatment-related AEs occurred less frequently in the nivolumab group: 58% any-grade and 7% grade 3 or 4 events compared with 86% any-grade and 55% grade 3 or 4 events in the docetaxel arm. The survival data were updated at the 2016 American Society of Clinical Oncology annual meeting, with the 1- and 2-year survival data for nivolumab being reported as 42% and 23% respectively compared with 24% and 8% for docetaxel[17].

CheckMate 057 was an international phase III randomized clinical trial comparing nivolumab with docetaxel in the second-line setting in patients with advanced nonsquamous cell lung cancer[14]. The dose and schedule of nivolumab and docetaxel were the same as those used in the CheckMate 017 trial. The median OS (mOS) was superior in the nivolumab arm (12.2 months vs. 9.4 months; HR: 0.73; 96% CI: 0.59 to 0.89; $p < 0.002$). The OS rate was 51% at 12 months and 39% at 18 months in the nivolumab arm compared with 39% and 23% in the docetaxel arm. The ORR was 19% with nivolumab and 12% with docetaxel. Expression of PD-L1 was predictive of benefit. Efficacy was greater with nivolumab than with docetaxel for subgroups pre-specified by PD-L1 expression (≥1%, ≥5%, and ≥10%), but not for the groups whose tumours were PD-L1–negative at those cut-offs. Treatment-related AEs occurred less frequently in the nivolumab group (69% vs. 88% with docetaxel), and grades 3 and 4 toxicities occurred at rates of 10% and 54% respectively in the two groups.

Results of the 3-year efficacy and safety data from both second-line trials were recently presented, showing ongoing progression-free survival (PFS) and OS benefits with nivolumab for both the squamous and nonsquamous histologies[18]. The 3-year OS rates for CheckMate 017 and CheckMate 057 were found to be 16% and 18% respectively,

TABLE I Agents targeting PD-1 or PD-L1 approved by the U.S. Food and Drug administration in the second-line setting

Characteristic	Agent			
	Nivolumab		Pembrolizumab	Atezolizumab
Target	PD-1		PD-1	PD-L1
Class	IgG4 fully human antibody		IgG4 humanized antibody	IgG1 humanized antibody
Company	Bristol–Myers Squibb		Merck	EMD/Pfizer
Phase III trial	CheckMate 017[13]	CheckMate 057[14]	KEYNOTE 010[15]	OAK[16]
Histology	Squamous	Nonsquamous	All	All
PD-L1 assessment	Retrospective	Retrospective	PD-L1≥1%	Stratified by PD-L1, but not required to be positive
Comparator	Docetaxel	Docetaxel	Docetaxel	Docetaxel

IgG = immunoglobulin G.

and of the patients who had responded to nivolumab, 26% and 23% respectively showed ongoing tumour responses. No new safety signals were identified with longer follow-up.

The international open-label phase II/III KEYNOTE 010 trial randomized patients 1:1:1 to receive pembrolizumab 2 mg/kg (n = 345), pembrolizumab 10 mg/kg (n = 346), or docetaxel 75 mg/m^2 (n = 343) every 3 weeks[15]. Eligibility required that patients have tumours expressing PD-L1. Treatment was continued for 24 months or until progressive disease or toxicity, and therapy beyond progression was permitted. The study had co-primary endpoints of OS and PFS in both the overall study population and the cohort with strong PD-L1 expression (≥50%), based on the potential association between higher PD-L1 expression and greater clinical benefit from pembrolizumab. In the overall study population, OS was superior for either dose of pembrolizumab compared with docetaxel, the mOS being 10.4 months for pembrolizumab 2 mg/kg (HR: 0.71; 95% CI: 0.58 to 0.88; $p < 0.0008$), 12.7 months for pembrolizumab 10 mg/kg (HR: 0.61; 95% CI: 0.49 to 0.75; $p < 0.0001$), and 8.5 months for docetaxel. The PFS did not differ significantly. Patients with the highest tumour expression of PD-L1 (≥50%) experienced greater benefit with pembrolizumab, the mOS being 14.9 months in the 2 mg/kg arm (HR: 0.54; 95% CI: 0.38 to 0.77; $p < 0.0002$), 17.3 months in the 10 mg/kg arm (HR: 0.50; 95% CI: 0.63 to 0.70; $p < 0.0001$), and 8.2 months with docetaxel. The median PFS (mPFS) was statistically improved in the patients treated with pembrolizumab when the expression of PD-L1 was 50% or greater. Tolerability was improved for patients receiving pembrolizumab compared with those receiving docetaxel; grade 3 or greater toxicities occurred at a frequency of 13% with pembrolizumab 2 mg/kg, 16% with pembrolizumab 10 mg/kg, and 35% with docetaxel.

The international phase III OAK trial evaluated the efficacy and safety of atezolizumab compared with docetaxel[16] in patients with advanced squamous and nonsquamous lung cancer after progression on platinum-doublet chemotherapy. Tissue was analyzed prospectively, and randomization was stratified by PD-L1 expression, although PD-L1 expression was not a requirement for eligibility. Patients were randomized to receive either atezolizumab 1200 mg (n = 425) or docetaxel 75 mg/m^2 (n = 425) every 3 weeks. The OAK trial had co-primary endpoints of OS in the intention-to-treat and PD-L1–expressing population [defined as ≥1% PD-L1 expression on tumour cells and immune cells by the Ventana SP142 assay (Ventana Medical Systems, Tucson, AZ, U.S.A.)]. In the intention-to-treat population, mOS was greater with atezolizumab (13.8 months) than with docetaxel (9.6 months; HR: 0.73; 95% CI: 0.62 to 0.87; p = 0.0003), a benefit that was evident regardless of PD-L1 expression. Survival was improved in the PD-L1–positive population (mOS: 15.7 months vs. 10.3 months; HR: 0.74; 95% CI: 0.58 to 0.93; p = 0.0102) and in patients with low or undetectable PD-L1 expression (mOS: 12.6 months vs. 8.9 months; HR: 0.75; 95% CI: 0.59 to 0.96; p = 0.0215). The greatest benefit was again seen in the patients with tumours having the highest PD-L1 expression (OS: 20.5 months vs. 8.9 months; HR: 0.41; 95% CI: 0.27 to 0.64; $p < 0.0001$) and was also evident regardless of tumour histology, with a HR for OS of 0.73 in both the squamous and nonsquamous subgroups. Notably, 17% of the patients treated with docetaxel subsequently received cancer immunotherapy, which might have led to increased survival in the docetaxel group and a reduction in the measured OS difference between the two groups. Atezolizumab was better tolerated overall, with fewer treatment-related AEs (15% vs. 43% with docetaxel).

The foregoing trials showed consistent improvement in ORR and OS with PD-1 or PD-L1 immunotherapy compared with standard chemotherapy, a benefit that was seen regardless of histology. The trials were also consistent in showing significantly less toxicity in patients receiving immunotherapy (Table II). Although the magnitude of the benefit appeared greatest in patients with tumours expressing high levels of PD-L1, the role of PD-L1 expression in selecting patients for second-line immunotherapy remains unclear.

Notably, the trials showed heterogeneity in terms of the cut-offs and methods used for PD-L1 testing and the determination of PD-L1 positivity based on the various assays. Many different antibodies, developed in conjunction with the different checkpoint inhibitors, are used to assay PD-L1. The Dako platform (Dako Corporation, Glostrup, Denmark) was used to develop the 22C3, 28-8, and 7810 antibodies in conjunction with pembrolizumab, nivolumab, and avelumab respectively. The Ventana platform (Ventana Medical Systems) was used to develop the SP142

TABLE II Adverse events related to therapy

Adverse event type	Occurrence by agent and trial arm (%)								
	Nivolumab				Pembrolizumab			Atezolizumab	
	CheckMate 017[17]		CheckMate 057[14]		KEYNOTE 010[15]			OAK[16]	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Pembro 2	Pembro 10	Docetaxel	Atezolizumab	Docetaxel
All grades	58	86	69	88	63	66	81	64	86
Grade 3 or greater	7	57	10	54	13	16	35	15	43
Led to discontinuation	3	10	5	15	4	5	10	8	19
Pneumonitis	5		3		5	4		1	
Hepatitis	2		<1		<1	1		0.3	
Colitis	1		1		1	<1		0.3	

Pembro = pembrolizumab (2 mg or 10 mg).

and SP263 antibodies in conjunction with atezolizumab and durvalumab respectively. Studies are under way to determine the consistency of PD-L1 identification with the various assays. The phase I Blueprint PD-L1 IHC Assay Comparison Project was developed to provide information about four commonly used PD-L1 immunohistochemical assays, finding that the 28-8, 22C3, and SP263 antibodies are comparable when staining tumour cells, with SP142 showing greater variability and fewer stained cells overall[19]. The latter finding is supported by another study that suggested that SP142 might have higher specificity, but lower sensitivity, when compared with 22C3 and that it typically underestimated PD-L1 scores for treatment with pembrolizumab[20]. A prospectively designed, statistically powered trial assessed 4 assays, including 22C3, E1L3N, 28-8, and SP142, and found the SP142 assay to be an outlier, detecting significantly less PD-L1 expression in tumour cells; however, excellent concordance and reproducibility between the other 3 assays was demonstrated, with the authors concluding that they were equivalent[21]. Although excellent concordance was seen when samples were obtained from tumour cells, greater variability was observed when scoring immune cells with any antibody[20,21].

Other factors are thought to contribute to predicting checkpoint inhibition response. The factor that has most clearly been studied is tumour mutational burden, with a higher nonsynonymous mutational burden having been discovered to be associated with improved ORR, durable clinical benefit, and PFS in NSCLC[22]. The whole-genome sequencing conducted during that study by Rizvi and colleagues discovered that efficacy was also correlated with molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations. A new blood-based assay for measuring tumour mutational burden was assessed retrospectively using plasma samples from the POPLAR and OAK trials, and the results were presented at the 2017 European Society for Medical Oncology annual meeting[23]. The assay found that a tumour mutational burden cut-point of 16 or greater correlated with PFS in patients on immunotherapy, potentially presenting another biomarker for predicting response that is not tissue-dependent. Other potential biomarkers that are currently under investigation include other checkpoint molecules, tumour-infiltrating lymphocytes and other components of the tumour microenvironment, and inflammatory gene signatures. Although the concept of microsatellite instability has been informative in colorectal cancer, its clinical relevance in NSCLC is not as well understood. A recent large study suggested that high microsatellite instability correlates strongly with high tumour mutational burden, independent of tumour histology[24].

FIRST-LINE TRIALS

Perhaps one of the most exciting developments in the realm of immunotherapy in NSCLC is the potential to replace chemotherapy with a more effective immunotherapy option in a select group of treatment-naïve patients. In the international phase III KEYNOTE 024 trial, pembrolizumab 200 mg every 3 weeks ($n = 154$) was compared with investigator's choice of platinum-doublet chemotherapy ($n = 150$) in patients with advanced NSCLC regardless of histology[25].

Traditionally, dosing of monoclonal antibodies has been weight-based because of thoughts about the contribution of body size to pharmacokinetic variability. However, in the case of pembrolizumab, the pharmacokinetic data have shown that doses of 200 mg and 2 mg/kg provide similar exposure distributions[26]. Patients were selected for tumour PD-L1 expression of 50% or greater and an absence of target mutations. Treatment in the pembrolizumab arm was continued for a total of 35 cycles, and platinum-doublet chemotherapy for 4–6 cycles, until progression or toxicity. Pemetrexed maintenance was allowed for patients with nonsquamous disease. Crossover from the chemotherapy arm to pembrolizumab at the time of confirmed progression was allowed. The primary endpoint was PFS [by independent review per RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1].

The trial met its primary endpoint with a mPFS of 10.3 months for pembrolizumab compared with 6.0 months for standard chemotherapy (HR: 0.50; 95% CI: 0.37 to 0.68; $p < 0.001$). A significant improvement in OS with pembrolizumab was also observed (HR: 0.60; 95% CI: 0.41 to 0.89; $p = 0.005$), and the ORR was higher in the pembrolizumab arm than in the chemotherapy arm (44.8% vs. 27.8%).

Pembrolizumab was also better tolerated, with any-grade AEs occurring in 73.4% of patients compared with 90.0% of those receiving chemotherapy, and grade 3 or greater AEs occurring in 26.6% compared with 53.3%. More immune-related AEs occurred in the pembrolizumab arm (all-grade AEs: 29.2% vs. 4.7%; grades 3 and 4 AEs: 9.7% vs. 0.7%).

Based on those results, the U.S. Food and Drug Administration approved the use of pembrolizumab as first-line therapy for patients with advanced NSCLC and tumours with PD-L1 expression of at least 50%. The KEYNOTE 024 trial was updated at the 2017 meeting of the International Association for the Study of Lung Cancer. The mos in the pembrolizumab arm was a remarkable 30 months, more than double the duration seen with standard chemotherapy (14.2 months)[27].

In contrast, the results with first-line nivolumab were not as promising. In the international phase III CheckMate 026 trial, nivolumab 3 mg/kg every 2 weeks (n = 271) was compared with investigator's choice of platinum-doublet chemotherapy (n = 270) in patients with metastatic or recurrent any-histology NSCLC[28]. Patients must also have had tumours with at least 1% PD-L1 expression by central review, but stratification was based on 5% or greater PD-L1 expression. The primary endpoint was PFS (by independent review per RECIST version 1.1) in patients with 5% or greater PD-L1 expression. The trial did not meet its primary endpoint, the PFS being 4.2 months compared with 5.9 months for platinum-doublet chemotherapy (HR: 1.15; 95% CI: 0.91 to 1.45; p = 0.25). No significant difference in OS between the arms was observed (HR: 1.02; 95% CI: 0.80 to 1.30). The treatment characteristics of the patients in the immunotherapy and chemotherapy arms showed notable differences, including the presence in the chemotherapy arm of more woman (45% vs. 32%) and more patients with 50% or greater PD-L1 expression. And even in patients with PD-L1 expression of at least 50%, no difference in PFS or OS was observed. Moreover, that subgroup still showed a pronounced sex imbalance, with the presence of more women having high PD-L1 expression in the chemotherapy arm (44% vs. 25%). Poor sex stratification could potentially have led to better outcomes in the chemotherapy arm than had been anticipated. Nivolumab was better tolerated, with fewer any-grade and grades 3 and 4 toxicities. Although CheckMate 026 failed to show benefit for first-line nivolumab, it could be argued that the immunotherapy arm performed as well as standard chemotherapy, with significantly less toxicity.

The reasons for the difference in the results from these two first-line trials are unclear. It is possible that issues related to patient selection or to the evaluation of PD-L1, or differences between the two agents, might have contributed to the better results with pembrolizumab. Differences in patient characteristics might have played a role. The nivolumab trial included a higher percentage of never-smokers (11% vs. 3%), who perhaps had a lower tumour mutational load and therefore a lesser response to immunotherapy. Another difference between the patients in these trials was the radiation treatment that they had previously undergone. Many of the nivolumab trial participants (37.6%) had already received radiation therapy; in the pembrolizumab trial, patients who had received more than 30 Gy within the first 6 months of trial therapy were excluded. That factor is an important one, because there is some thought that prior radiation therapy can have consequences for the tumour microenvironment, leading to a decreased response to checkpoint inhibition in previously irradiated sites[29]. Differences in biomarker tests for PD-L1 (22C3 for pembrolizumab, 28-8 for nivolumab) and the use of new tissue in the pembrolizumab trial compared with archival tissue in the nivolumab trial could also have contributed to some of the differences. A third phase III trial in the first-line setting, KEYNOTE 042 (see NCT02220894 at http://ClinicalTrials.gov) is randomizing patients with tumours expressing at least 1% PD-L1 to pembrolizumab or to standard platinum-doublet chemotherapy. The primary endpoint of this trial is OS in the population with strong PD-L1 expression. The trial might serve to confirm the benefits of pembrolizumab as initial therapy in the relevant population.

Although the focus of the present review is metastatic NSCLC, note should be taken of the recently published results of the PACIFIC trial. A phase III trial, PACIFIC was conducted in patients with locally advanced unresectable NSCLC who had been treated with curative-intent concurrent chemoradiotherapy; participants who did not experience progression after 2 or more cycles of platinum-based chemoradiotherapy then received up to 1 year of consolidative durvalumab 10 mg/kg twice weekly (n = 473) or placebo (n = 236)[30]. The co-primary endpoints were PFS and OS. The trial met its primary endpoint of PFS (16.8 months with durvalumab vs. 5.8 months with placebo; HR: 0.52; $p < 0.001$) in a biomarker-independent population, regardless of baseline expression of PD-L1 on tumour cells. The 12-month PFS rates were 55.9% and 35.3% respectively, and the 18-month PFS rates were 44.2% and 27.0%. The ORR was also higher in the consolidation immunotherapy arm (28.4% vs. 16%), and interestingly, 72.8% of the patients receiving immunotherapy had an ongoing response at 18 months (suggestive of durable response) compared with 46.8% of the patients receiving placebo. Treatment was not associated with a higher cost to safety, because grade 3 and greater AEs were similar in both arms (29.9% vs. 26.1%). The trial also shed light on the incidence of pneumonitis with immunotherapy in patients who had received thoracic radiation, finding that particular AE to be mostly low-grade, with grade 3 and greater events occurring at similar rates in the two groups. Data for OS were not mature at the time of the interim analysis.

COMBINATION THERAPY TRIALS

The trials discussed so far have led to the establishment of single-agent PD-1 or PD-L1 immunotherapy as a new standard of care in the second-line therapy of advanced NSCLC, and to the approval in the United States and Europe of pembrolizumab as first-line therapy for patients with tumours strongly expressing PD-L1 (≥50% staining). First-line pembrolizumab is now available in Canada with ministerial-approved funding. This advance in the management of NSCLC is significant; however, most patients will not benefit from single-agent therapy. A number of strategies to improve outcomes with immunotherapy are

being evaluated. Combining PD-1 or PD-L1 immunotherapeutic agents with standard chemotherapy or with CTLA-4 therapies are the two main strategies being pursued.

Several conventional chemotherapy agents used to treat solid tumours have been shown to have immunostimulatory properties[31]. Phase I trials combining PD-1 or PD-L1 agents with various platinum-doublet regimens have been shown to be tolerable and to have promising activity (Table III).

The multi-cohort phase I/II KEYNOTE 021 investigated the efficacy and safety of adding pembrolizumab to several chemotherapy regimens[33]. Based on the tolerability and activity of pembrolizumab–platinum–pemetrexed, that combination was expanded to a randomized phase II trial[35]. Patients were stratified by PD-L1 score (<1% vs. ≥1%) and then randomized to receive pembrolizumab 200 mg, carboplatin area under the curve 5, and pemetrexed 500 mg/m^2 every 3 weeks, followed by pembrolizumab for 24 months and pemetrexed until progression or toxicity, or the same carboplatin and pemetrexed chemotherapy alone. Crossover from the chemotherapy arm to pembrolizumab was permitted at progression. The primary endpoint was ORR (independently assessed according to RECIST version 1.1).

The arm with the added pembrolizumab showed an improved ORR (55% vs. 29% with chemotherapy alone, p = 0.0016). The subgroup analysis based on PD-L1 stratification showed similar ORR results (57% for those scoring <1% and 54% for those scoring ≥1%, p = 0.0016). In the arm with the added pembrolizumab, the ORR was 80% in patients with 50% or greater PD-L1, and the mPFS was significantly longer at 13.0 months compared with 8.9 months for chemotherapy alone (HR: 0.53; 95% CI: 0.31 to 0.91; p = 0.010). Median follow-up was short at 10.6 months, and 74% of patients who discontinued therapy in the chemotherapy-only arm subsequently received immunotherapy, which could have accounted for the lack of a statistically significant difference in OS at the time of reporting. No significant difference in grade 3 toxicities was observed between the two groups (39% for added pembrolizumab vs. 26% for chemotherapy alone).

The trial was updated at the 2017 meeting of the International Association for the Study of Lung Cancer. The HR in favour of the combination arm continues to improve (HR: 0.59; 95% CI: 0.34 to 1.05), although not statistically significantly[36]. The improvements in ORR (57% vs. 32%) and mPFS (19 months vs. 8.9 months) are being maintained. A randomized phase III trial, KEYNOTE 189 (see NCT02578680 at http://ClinicalTrials.gov), will compare platinum–pemetrexed with and without pembrolizumab with a primary endpoint of PFS.

The PD-1 and CTLA-4 checkpoints use distinct mechanisms to modulate T-cell function. A combination of agents targeting those distinct mechanisms might improve antitumour immune response, but at the risk of increased immune-related toxicity[37]. Phase I trials of nivolumab with ipilimumab[38] and durvalumab with tremelimumab[39] have been published. Those trials focused on defining tolerable doses and schedules of combination immunotherapy. In general, toxicity was limited by the dose and frequency of the CTLA-4 agent. Regimens with tolerable safety profiles were established for both combinations, but their toxicity is higher than that seen with anti–PD-1 or –PD-L1 monotherapy. Clinical activity was seen in both PD-L1–positive and –negative patients, but the numbers of patients in those subgroups have been too small to allow for firm conclusions to be drawn about the patients who might benefit most. In NSCLC, doses for combination regimens include nivolumab at 3 mg/kg every 2 weeks, and ipilimumab at 1 mg/kg every 12 weeks[38]. Those doses contrast with the doses in small-cell lung cancer, where studies have used nivolumab 1 mg/kg plus ipilimumab at 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks[40]. That schedule is akin to those used in the initial trials of combination immunotherapy in patients with metastatic melanoma[41].

Most recently, the results of the phase III MYSTIC trial, which compared both durvalumab monotherapy and durvalumab in combination with tremelimumab with the platinum-doublet standard of care in the first-line setting in patients with 25% or greater PD-L1 expression as assessed

TABLE III Combination immunotherapy plus chemotherapy in the first-line setting

Trial	Agents		Pts (*n*)	ORR (%)
	Immunotherapy	Chemotherapy		
GP28328[32]	Atezolizumab	Carboplatin–paclitaxel	8	50
		Carboplatin–pemetrexed	17	77
		Carboplatin–nab-paclitaxel	16	56
KEYNOTE 021[33]	Pembrolizumab	Carboplatin–paclitaxel with bevacizumab	25	52
		Carboplatin–paclitaxel	25	48
		Carboplatin–pemetrexed	24	71
CheckMate 012[34]	Nivolumab			
	(10 mg)	Cisplatin–gemcitabine	12	33
	(10 mg)	Cisplatin–pemetrexed	15	47
	(10 mg)	Carboplatin–paclitaxel	15	47
	(5 mg)	Carboplatin–paclitaxel	14	43

ORR = objective response rate.

by SP263 assay, were reported (AstraZeneca press release, 2017[42]). The trial did not meet its primary endpoint of improved PFS compared with the standard of care in either the monotherapy or combination immunotherapy arm. The OS data were still immature at the time of reporting and should be available in 2018.

Several trials are ongoing, investigating combination checkpoint inhibitors and combinations of PD-1 or PD-L1 agents with chemotherapy (Table IV). Given that the costs and toxicity with combination therapy are greater than those with anti–PD-1 or –PD-L1 monotherapy, those trials will be important in defining the populations that will derive additional benefit from combination immunotherapy, and in better defining the toxicities of combination therapy.

It seems that CTLA-4, PD-1, and PD-L1 are only the beginning for this class of agents; many other immunomodulatory agents are currently under development as single agents or in combination with PD-1 and PD-L1 inhibitors. Examples include LAG-3 (an inhibitory receptor signalling anergy and exhaustion), VISTA, and Tim-3. The other class of antibodies gaining traction are immunostimulatory molecules such as anti-CD40, anti–4-1BB (CD137), and OX40 (CD134) which promote activation of effector cells or antigen-presenting cells[43].

SUMMARY OF THE CURRENT LANDSCAPE

The discovery of immune checkpoint inhibitors has dramatically changed the treatment landscape for patients with advanced NSCLC. Studies involving monoclonal antibodies directed at the PD-1–PD-L1 axis have introduced new therapeutic targets that show effective antitumour activity in a proportion of patients and potentially durable responses. Three agents have been approved for use in second-line therapy, and pembrolizumab has been shown to be superior to standard platinum-doublet chemotherapy in patients with tumours strongly expressing PD-L1. The results from phase I and II trials of combination immunotherapy and of chemotherapy plus immunotherapy have been encouraging and suggest that those strategies might extend the benefits of immunotherapy to more patients. It is critical that investigators enrol patients to clinical trials that address the issues of which patients benefit most from PD-1 and PD-L1 monotherapy, combination checkpoint therapy, and combination chemoimmunotherapy.

A presentation at the annual meeting of the American Association for Cancer Research[44] describing the 5-year follow-up of patients treated in the CheckMate 003 trial highlights the true promise of immunotherapy. In this trial of patients with pretreated advanced NSCLC who received up to 92 weeks of single-agent nivolumab and who were followed for a minimum of 58 months, a plateau in the survival curve was observed. The 5-year OS was 16% for a disease in which the expected 5-year survival is less than 5%. In patients with tumours expressing 50% or more PD-L1, the 5-year OS was an astonishing 43%. Those results raise, for the first time, the hope that patients with advanced NSCLC might look forward to years of survival.

TABLE IV Upcoming and ongoing clinical trials using immunotherapy in non-small-cell lung cancer

Line of therapy	Strategy	Trial name	Therapy arms	Phase
First line				
	Monotherapy (IO or CTx)	KEYNOTE 042	Pembrolizumab vs. platinum doublet (PD-L1–positive)	
		IMpower 110	Atezolizumab vs. platinum doublet	
		IMpower 111	Atezolizumab vs. platinum–gemcitabine (squamous)	
		JAVELIN LUNG 100	Avelumab vs. platinum doublet (PD-L1–positive)	
	IO–CTx	CheckMate 227	Nivolumab or nivolumab–ipilimumab or nivolumab plus platinum doublet chemotherapy vs. platinum doublet chemotherapy (PD-L1–positive and –negative populations)	III
		KEYNOTE 189	Platinum–pemetrexed with or without pembrolizumab	III
		IMpower 130	Atezolizumab with carboplatin–nab-paclitaxel vs. carboplatin–nab-paclitaxel (nonsquamous)	
		IMpower 131	Atezolizumab with carboplatin–nab-paclitaxel vs. carboplatin–nab-paclitaxel (squamous)	
		IMpower 150	Atezolizumab with carboplatin–paclitaxel with or without bevacizumab vs. carboplatin–paclitaxel with bevacizumab (nonsquamous)	
	IO–IO	MYSTIC	Durvalumab with or without tremelimumab vs. platinum doublet chemotherapy	III
		CheckMate 227	Nivolumab or nivolumab–ipilimumab or nivolumab plus platinum doublet chemotherapy vs. platinum doublet chemotherapy (PD-L1–positive and –negative populations)	III
		NEPTUNE	Durvalumab–tremelimumab vs. platinum doublet chemotherapy	II
Previously treated				
	IO–IO	ARCTIC	Durvalumab vs. standard of care chemotherapy (PD-L1–positive)	
			Durvalumab–tremelimumab vs. standard of care chemotherapy (PD-L1–negative)	III

IO = immunotherapy; CTx = chemotherapy.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: CAB has received honoraria from Bristol–Myers Squibb, AstraZeneca, and Merck. AP has received fees as an advisory board member for AstraZeneca.

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