

Tumour Review

PD-1 blockade in advanced NSCLC: A focus on pembrolizumab

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ABSTRACT

Non-small cell lung cancer (NSCLC) is one of the most prevalent cancers and is responsible for a large proportion of all cancer-related deaths. Current treatment options are inadequate, reflecting a substantial unmet clinical need. Increasing knowledge regarding the mechanisms and genetic aberrations underlying tumor development and growth has heralded a new era of therapy in oncology, moving away from indiscriminate cytotoxic chemotherapy toward more finely focused, targeted medicine. The development of small-molecule drugs and monoclonal antibodies directed toward specific components of dysfunctional molecular or immune pathways, and mutated genes specific to particular cancer types, is leading the field to more personalized and less toxic treatment options, many of which have demonstrated greater efficacy and survival benefits than their chemotherapeutic counterparts. Particularly successful examples are agents that interfere with the programmed death 1 (PD-1) pathway, which many tumors can hijack to avoid immune surveillance and editing. Pembrolizumab, a monoclonal antibody directed at PD-1 that blocks the engagement between PD-1 and its ligands, has been explored as a treatment for solid tumors, and demonstrated survival benefits in several studies. The use of PD-1 inhibitors such as nivolumab and pembrolizumab in advanced cancers is widespread, and pembrolizumab is available in more than 60 countries for at least one of the following: advanced melanoma, PD-L1-expressing NSCLC, head and neck squamous cell carcinoma, and adult and pediatric patients with refractory classical Hodgkin's lymphoma. This work provides a brief overview of the role of pembrolizumab in the treatment of advanced (recurrent/metastatic) NSCLC.

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Introduction

Lung cancer is a major worldwide health problem, with an estimated 1.8 million new cases globally in 2012, representing 12.9% of all new cancer cases [1]. There are two main subsets of lung cancer: small cell lung cancer (SCLC) and non-SCLC (NSCLC); NSCLC, as a group of different cancers, comprises approximately 85% of all lung cancers, with an estimated 1.55 million new cases globally in 2012 [1,2]. Lung cancer was responsible for the highest number of cancer deaths worldwide in 2012, estimated at 1.59 million, which represents 19.4% of all cancer deaths. That figure is more than twice the number attributable to the second most common cause of cancer deaths—liver cancer (745,000 deaths) [1]. The highest number of cancer deaths for both sexes in the United States and Europe is attributed to lung cancer, and in Europe, lung cancer accounts for more than the total number of deaths from colorectal

and breast cancer combined [1]. These statistics highlight the substantial global burden associated with lung cancer, and NSCLC in particular, and emphasize the need for novel treatment approaches.

Current treatment recommendations

First-line therapy

Traditionally, the standard first-line treatment for NSCLC has been platinum-based combination doublet chemotherapy regimens, and although none was found to be superior to the other [3], frequently used first-line treatments in the United States are gemcitabine + cisplatin for squamous cell carcinoma and cisplatin (or carboplatin) + pemetrexed or carboplatin + paclitaxel (+bevacizumab) for non-squamous NSCLC [4]. Cisplatin + pemetrexed is the preferred treatment recommended in the European Society for Medical Oncology (ESMO) guidelines for the first-line treatment of non-squamous NSCLC patients younger than 70 years of age with an ECOG performance status of 0–1 [5]. Bevacizumab should

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be considered in conjunction with carboplatin + paclitaxel for patients with advanced NSCLC and Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1 [5]. If platinum therapy is contraindicated, then non-platinum-based chemotherapy with third-generation agents such as gemcitabine, vinorelbine, and taxanes can be considered [4,5]. Maintenance chemotherapy with pemetrexed is recommended for patients with an ECOG PS score of 0–1 and partial response or stable disease after first-line therapy [5]. Phase III clinical studies examining the different regimens and duration of platinum-based combination therapies demonstrated dismal median progression-free survival (PFS) and overall survival (OS) times of approximately 4–8 and 6–16 months, respectively [3,6], with 1-year OS rates as low as 30–40%. Therefore, therapies that improve PFS and OS are warranted.

Second-line therapy

Treatment options for patients who experience relapse or become resistant to first-line therapies include chemotherapeutics such as docetaxel and pemetrexed, which are approved as second-line therapies for the treatment of locally advanced or metastatic NSCLC [7–9]. In Europe, pemetrexed is generally used as first-line therapy for non-squamous NSCLC [5]; therefore, docetaxel is the only approved chemotherapy option for patients who experience disease progression on pemetrexed. Although docetaxel is associated with response rates of around 10% and 1-year survival rates of 30–40%, it is associated with serious toxicity [10–12]. Lack of options for second-line therapy in patients who do not respond to or who experience progression on first-line therapy has been a concern for many clinicians.

Targeted therapy in NSCLC

Over the past decade, several targeted therapies for NSCLC have been developed, almost exclusively targeting adenocarcinoma, characterized by mutations of the gene encoding epidermal growth factor receptor (*EGFR*) and rearrangement of those encoding anaplastic lymphoma kinase (*ALK*) and *c-ros* oncogene 1 (*ROS1*) [13]. Activating *EGFR* mutations occur in 10–60% of patients with NSCLC, with higher frequencies occurring in Asian populations, never smokers and among females compared with males [14,15], and *ALK* translocations occur in 2–20% of patients and result in increased cellular proliferation and thereby tumorigenesis [16–18]. The benefit of targeted therapies in patients with these two genetic aberrations is such that biomarker testing is now recommended as part of the pathology workup for all patients with NSCLC [4,5].

As of 2016, *EGFR* inhibitors recommended for the treatment of NSCLC include erlotinib, afatinib, or gefitinib [4,5]. However, a common limitation of *EGFR* tyrosine kinase inhibitors (TKIs) is acquired resistance after a median of 9–13 months [19], highlighting the need for the development of additional novel targeted drug treatments such as osimertinib against NSCLC with the acquired *EGFR* mutation T790M [20]. The T790M mutation accounts for the TKI resistance in about 60% of relapsing patients [21].

Crizotinib is indicated as a first-line treatment in both Europe and the United States for NSCLC in patients with *ALK* (or *ROS1*) translocation identified before first-line chemotherapy [4,5,22,23]. As with *EGFR*-TKIs, patients ultimately develop resistance to *ALK* inhibitors, usually within 1–2 years [17]. Recent approval of ceritinib and alectinib for patients who experience disease progression with or who are intolerant of crizotinib therapy and development of additional *ALK* inhibitors are promising developments [24–28]. Of note, alectinib was recently shown to repre-

sent a new standard of care frontline, with significantly better PFS outcome and central nervous system control as compared with crizotinib [29]. Many other driver oncogenes are being evaluated as treatment targets in NSCLC, including *MET*, *HER2*, *BRAF*, and *KRAS* mutations, as well as *RET* and *NTRK* rearrangements [30].

The PD-1 pathway and NSCLC

Failure to mount an effective antitumor immune response is a characteristic of cancer growth and progression [31]. PD-1 is highly expressed on the surface of activated T cells in response to inflammation or infection, acting as an “immune checkpoint.” Tumor cells can evade the immune response through the upregulated expression of PD-L1.

When bound to its ligand PD-L1, the complex PD-1/PD-L1 acts to inhibit the immune response by inhibiting the cytotoxic T-cell response (Fig. 1) [31–33]. Tumor cells can utilize this pathway to promote immunosuppression, thereby evading antitumor activity. PD-1 or PD-L1 inhibitors disrupt this inhibitory T-cell signaling, thus reactivating the antitumor activity of specific cytotoxic T cells [31,32]. Up to 68% of NSCLC tumors have been shown to express PD-L1 [34,35]. Recently, there has been enormous activity in investigating targeting of the PD-1 pathway using monoclonal antibodies raised against not only the PD-1 protein, but also its ligand PD-L1, as a treatment for several distinct advanced malignancy, including NSCLC (Fig. 2) [34].

The immune checkpoint inhibitors nivolumab, pembrolizumab (which target the PD-1 pathway), and atezolizumab (which targets PD-L1) have been approved by regulatory authorities [36–41]. In the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology NSCLC treatment guidelines, anti-PD-1 inhibitors are currently recommended for subsequent treatment of patients with disease progression on or after first-line chemotherapy [4,5], and in the NCCN guidelines as a first-line therapy in strongly PD-L1-expressing tumors with no *EGFR* or *ALK* genomic aberrations [4]. Table 1 summarizes the studies that supported regulatory approval for these agents. The pivotal studies resulting in the US Food and Drug Administration (FDA)/European Medicines Agency (EMA) approval of pembrolizumab for NSCLC and ongoing studies in patients with lung cancer will be discussed.

Pembrolizumab

Pembrolizumab is a humanized immunoglobulin (Ig) G4 kappa PD-1 monoclonal antibody that first received FDA approval in the United States in 2014, then in Europe by the EMA in 2015, for the treatment of treatment-refractory melanoma [36,42,43]. Pembrolizumab was granted FDA breakthrough therapy designation for the treatment of advanced NSCLC in 2014, FDA approval in 2015, and EMA approval in 2016 for the treatment of metastatic NSCLC with PD-L1 expression and progression on or after platinum-based chemotherapy (or FDA-approved *EGFR*- or *ALK*-targeting therapy, where applicable) [36,44]. Pembrolizumab is recommended in the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines for the treatment of patients with advanced NSCLC with PD-L1 expression (level of recommendation category 1) [4,5]. Recently, it was approved by the FDA, EMA, and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of patients with metastatic NSCLC and high PD-L1 expression [tumor proportion score (TPS) ≥50%] with no *EGFR* or *ALK* genomic tumor aberrations and no prior chemotherapy [40,41,45].

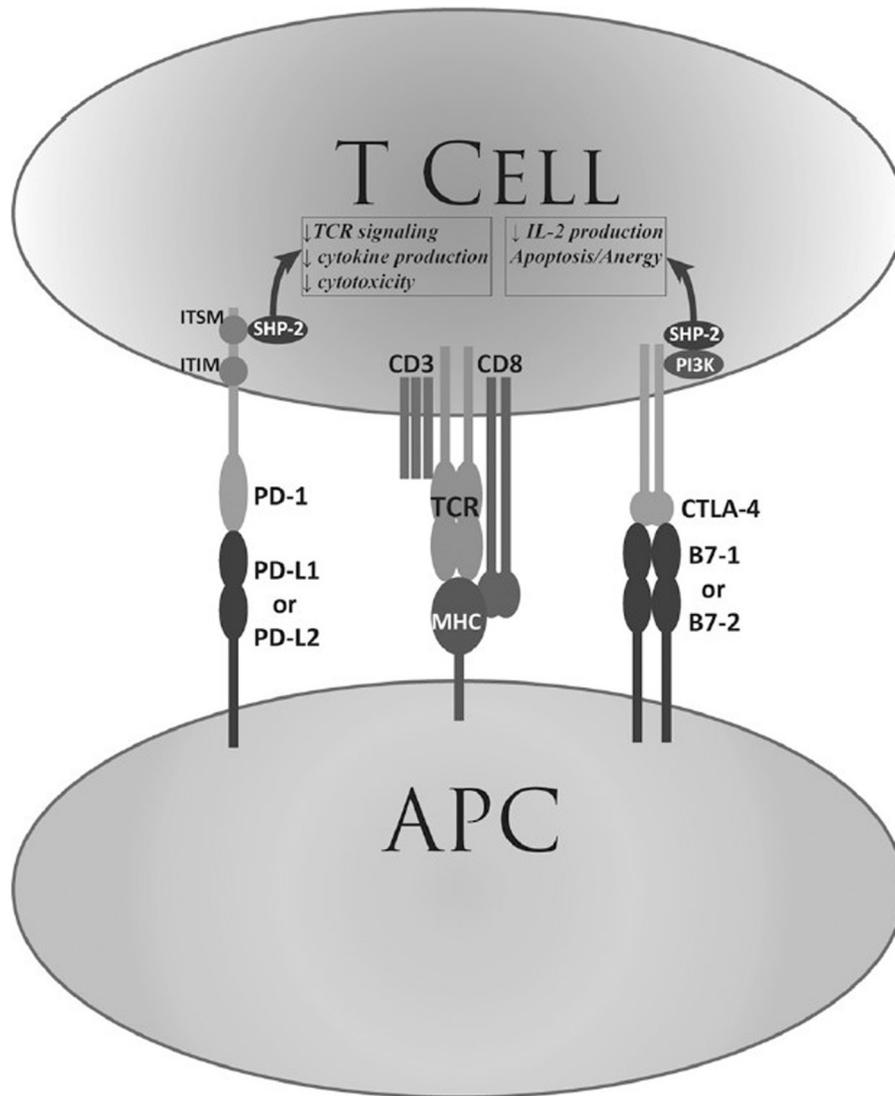


Fig. 1. The function of PD-1 in T-cell signaling [33]. APC = antigen-presenting cell; IL-2 = interleukin 2; ITIM = immunoreceptor tyrosine-based inhibitory motif; ITSM = immunoreceptor tyrosine-based switch motif; MHC = major histocompatibility complex; PD-1 = programmed death 1; PD-L1/L2 = programmed death ligand 1/2; PI3K = phosphoinositide 3-kinase; SHP-2 = cytoplasmic SH2 domain containing protein tyrosine phosphatase; TCR = T-cell receptor. Republished with permission of American Society of Hematology from Armand P. *Blood* 2015;125:3393–400. Permission conveyed through Copyright Clearance Center, Inc.

KEYNOTE-001

The phase I KEYNOTE-001 (ClinicalTrials.gov, NCT01295827) study was an international clinical trial that investigated the safety and antitumor efficacy of pembrolizumab in patients with solid tumors (including advanced NSCLC), in previously treated and untreated patients. Patients received pembrolizumab via intravenous administration at 2 mg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks. The study endpoints were safety, side effect profile, and efficacy (objective response rate [ORR], OS, PFS, duration of response [DOR], and disease progression) [31]. Observation of an association between PD-L1 expression and pembrolizumab efficacy [46] led to a protocol amendment of an additional primary endpoint evaluating efficacy in NSCLC patients with a high level of PD-L1 expression [31]; the findings related to PD-L1 expression will be discussed separately herein.

Pembrolizumab demonstrated a good safety profile with minimal toxicity in patients with NSCLC. Grade ≥ 3 adverse events were observed in 10% of patients. Treatment-related adverse events (TRAEs) were reported in 71% of patients

(70.9%), with no differences observed between dosage or dosing schedule [31].

The tolerable safety profile of pembrolizumab was coupled with promising efficacy. The ORR for the overall population with NSCLC, which included both treatment-experienced ($n = 394$) and treatment-naïve patients ($n = 101$) was 19% (95% confidence interval [CI] 16–23), with stable disease in 22% with no differences between dosage and dosing schedules for all patients. The ORR for the treatment-experienced (83% had received ≥ 2 prior lines of therapy) and naïve patients was 18% (95% CI 14–22) and 25% (95% CI 17–34), respectively. Median PFS and OS were 3.7 months (95% CI 2.9–4.1) and 12.0 months (95% CI 9.3–14.7), respectively, for the entire cohort [31]. In an updated survival analysis after a median follow-up of 22 months, median OS was 22.1 months (95% CI 16.8–27.2) in treatment-naïve patients and 10.6 months (95% CI 8.6–13.3) in previously treated patients [47].

The safety and efficacy findings of this phase I study prompted the initiation of additional phase I–III studies to further investigate the use of pembrolizumab as a single agent and in combination with other therapeutics in patients with NSCLC (Table 2), in partic-

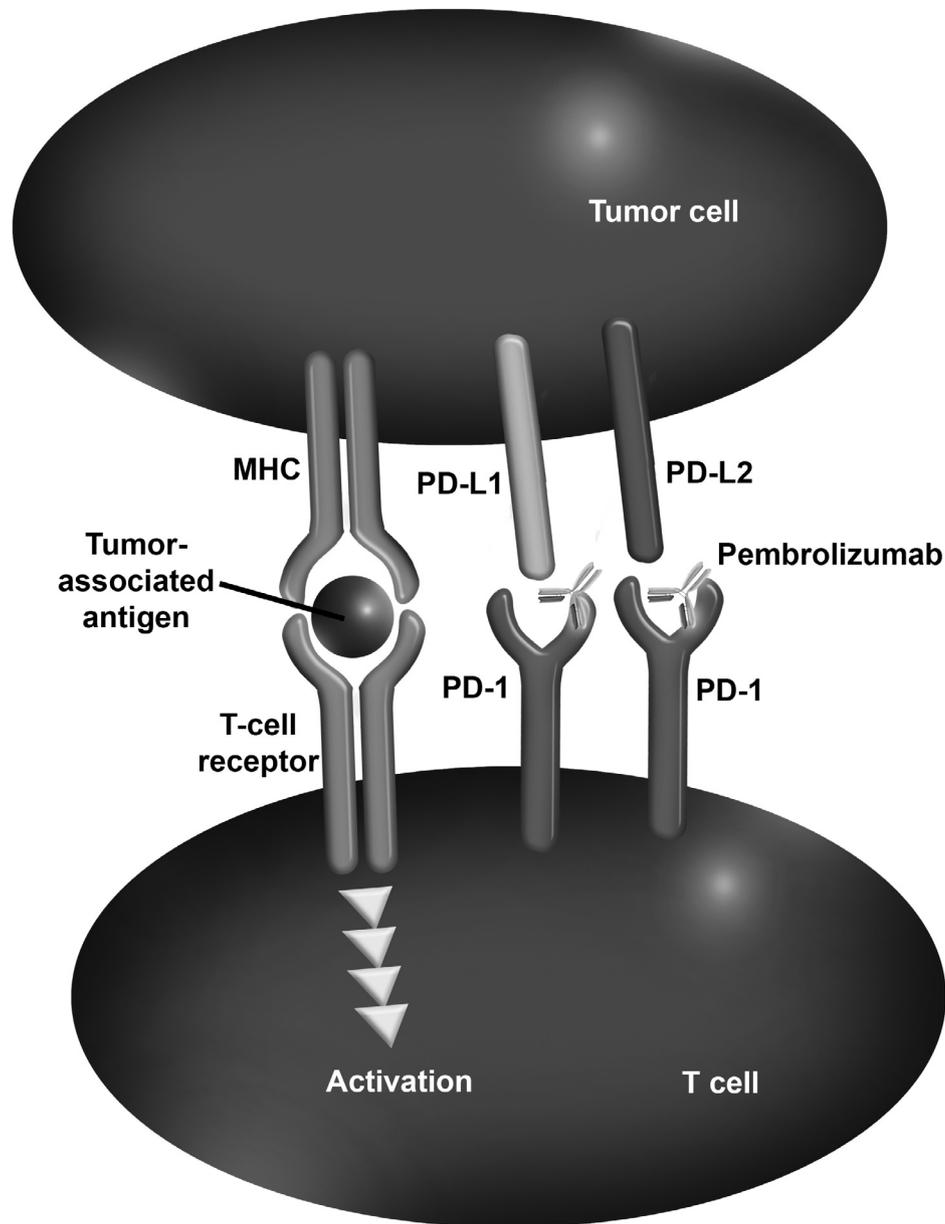


Fig. 2. Mechanism of action of the anti-PD-1 antibody pembrolizumab. MHC = major histocompatibility complex; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1.

ular the pivotal phase II/III KEYNOTE-010 trial (ClinicalTrials.gov, NCT01905657), the phase III KEYNOTE-024 trial (ClinicalTrials.gov, NCT02142738), and the phase I/II KEYNOTE-021 trial (ClinicalTrials.gov, NCT02039674) [48].

KEYNOTE-010

The KEYNOTE-010 study (NCT01905657) was a randomized, open-label, phase II and III clinical trial comparing the safety and efficacy of pembrolizumab with docetaxel in patients with NSCLC whose tumors express PD-L1. Patients were assigned to one of three treatment groups: pembrolizumab at 2 mg/kg ($n = 345$), 10 mg/kg ($n = 346$) every 3 weeks, or docetaxel 75 mg/m² ($n = 343$) every 3 weeks. The primary endpoints were OS and PFS in all patients and in the subset of patients whose tumors expressed higher levels of PD-L1; the relevance of PD-L1 expression and efficacy will be discussed in the “Role of PD-L1 as a predictive

biomarker” section. Secondary endpoints included safety, response rate, and DOR [49].

Pembrolizumab demonstrated an improved OS benefit at both tested doses in the total population compared with docetaxel. Median OS was 10.4 months (95% CI 9.4–11.9), 12.7 months (95% CI 10.0–17.3), and 8.5 months (95% CI 7.5–9.8) in the pembrolizumab 2-mg/kg, 10-mg/kg, and docetaxel treatment groups, respectively [49]. The hazard ratios (HRs) of pembrolizumab 2 mg/kg and 10 mg/kg versus docetaxel were 0.71 (95% CI 0.58–0.88; $P = .0008$) and 0.61 (95% CI 0.49–0.75; $P < .0001$), respectively. OS was similar regardless of pembrolizumab dose (HR 1.17; 95% CI 0.94–1.45) [49]. Differences in PFS were not statistically significant between either of the pembrolizumab doses and docetaxel (prespecified P value for significance; $P < .001$). The HR of pembrolizumab 2 mg/kg and 10 mg/kg versus docetaxel was 0.88 (95% CI 0.74–1.05; $P = .07$) and 0.79 (95% CI 0.66–0.94; $P = .004$); median PFS was 3.9 months (95% CI 3.1–4.1), 4.0 months

Table 1
Key clinical trials of PD-1 and PD-L1 inhibitors in patients with NSCLC.

Clinical trial	Treatment and comparator (if any)	Purposes	N	Efficacy results
<i>Nivolumab</i>				
CheckMate017 NCT01642004 phase III [79]	Nivolumab vs docetaxel	Compare OS of nivolumab and docetaxel in patients with squamous NSCLC after failure of prior platinum-based therapy	272	<ul style="list-style-type: none"> • Median OS 9.2 months with nivolumab vs 6.0 months with docetaxel; HR 0.59; 95% CI 0.44–0.79; $P < 0.001$ • OS at 1 year was 42% vs 24% • ORR was 20% vs 9% ($P = .008$) • Median PFS was 3.5 months vs 2.8 months; HR 0.62; 95% CI 0.47–0.81; $P < 0.001$ • PD-1 expression was not prognostic or predictive
CheckMate057 NCT01673867 phase III [76]	Nivolumab vs docetaxel	Compare OS of nivolumab and docetaxel in patients with non-squamous NSCLC after failure of platinum-based therapy	292	<ul style="list-style-type: none"> • Median OS was 12.2 months in nivolumab group vs 9.4 months in the docetaxel group; HR 0.73; 96% CI 0.59–0.89; $P = .002$ • OS rate at 1 year was 51% vs 39% • Response rate was 19% vs 12% ($P = .02$) • PFS was 2.3 months vs 4.2 months, but the rate of PFS at 1 year was greater with nivolumab (19%) than with docetaxel (8%) • In patients with $\geq 5\%$ PD-L1 expression ($n = 423$), median PFS was 4.2 months with nivolumab and 5.9 months with chemotherapy; HR 1.15; 95% CI 0.91–1.45; $P = .25$
CheckMate026 NCT02041533 phase III [81]	Nivolumab vs chemotherapy	Compare the PFS of nivolumab and investigator's choice of chemotherapy as first-line treatment in patients with PD-L1 + NSCLC	541	<ul style="list-style-type: none"> • In patients with $\geq 5\%$ PD-L1 expression ($n = 423$), median PFS was 4.2 months with nivolumab and 5.9 months with chemotherapy; HR 1.15; 95% CI 0.91–1.45; $P = .25$
<i>Pembrolizumab</i>				
KEYNOTE-001 NCT01295827 phase I [31]	Pembrolizumab	Assess safety and efficacy of pembrolizumab in patients with advanced NSCLC	495	<ul style="list-style-type: none"> • ORR 19.4% • Median PFS was 3.7 months • Median PFS in patients with $\geq 50\%$ TPS was 6.3 months • Median OS was 12.0 months
KEYNOTE-010 NCT01905657 phase II/III [49]	Pembrolizumab vs docetaxel	Compare the safety and efficacy of pembrolizumab and docetaxel in patients with previously treated NSCLC	1034	<ul style="list-style-type: none"> • Median OS was 10.4 months on 2 mg/kg pembrolizumab and 12.7 months with pembrolizumab 10 mg/kg vs 8.5 months with docetaxel • OS was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (HR 0.71; 95% CI 0.58–0.88; $P = .0008$) and 10 mg/kg (HR 0.61; 95% CI 0.49–0.75; $P < .0001$) • In patients with TPS $\geq 50\%$, OS was significantly longer with pembrolizumab than with docetaxel in both the 2 mg/kg dose (median 14.9 months vs 8.2 months; HR 0.54; 95% CI 0.38–0.77; $P = .0002$) and the 10 mg/kg dose (17.3 months vs 8.2 months; HR 0.50; CI 0.36–0.70; $P < .0001$)
KEYNOTE 021 cohort G [53] NCT02039674	Pembrolizumab in combination with chemotherapy or immunotherapy	Determine safety, tolerability, and efficacy of pembrolizumab in combination with chemotherapy or immunotherapy	123	<ul style="list-style-type: none"> • Objective response was reported in 18 of 63 patients in the chemotherapy group and 33 of 60 in pembrolizumab + chemotherapy arm; incidence of grade 3 or worse TRAE was similar between groups
KEYNOTE-024 NCT02142738 phase III [51]	Pembrolizumab vs platinum-based chemotherapies	Compare the efficacy and safety of pembrolizumab and platinum-based chemotherapies as first-line treatment in patients with PD-L1-expressing (TPS $\geq 50\%$) NSCLC	305	<ul style="list-style-type: none"> • Median PFS was 10.3 months (95% CI 6.7–NR) on pembrolizumab 200 mg Q3W vs 6.0 months (95% CI 4.2–6.2) for chemotherapy; HR 0.50; 95% CI 0.37–0.68; $P < .001$ • 6-month OS was 80.2% vs 72.4%; HR 0.60, 95% CI 0.41–0.89; $P = 0.005$ • ORR = 44.8% vs 27.8%
<i>Atezolizumab</i>				
POPULAR NCT01903993 phase II[35]	Atezolizumab vs docetaxel	Evaluate efficacy and safety of atezolizumab and docetaxel in patients with NSCLC after failure of platinum-containing chemotherapy	287	<ul style="list-style-type: none"> • ORR was the same with atezolizumab and docetaxel: $n = 21$ (15%) • Median PFS was 2.7 months for atezolizumab, 3.0 months for docetaxel • Median OS was 12.6 months vs 9.7 months ($P = .04$) • OS was significantly improved for all patients with any level of PD-L1 expression (in tumor cells or tumor-infiltrating immune cells) who received atezolizumab vs docetaxel
BIRCH NCT02031458 phase II [90]	Atezolizumab	Evaluate efficacy and safety of atezolizumab in patients with PD-L1-positive, locally advanced or metastatic NSCLC in first-, second- or later line (C1, C2, C3)	667	<ul style="list-style-type: none"> • ORRs in the C1, C2, and C3 subgroups ranged from 17% to 27% • 6-month PFS rates in C1, C2, and C3 were 29–48% • 6-month OS rates in C1, C2, and C3 were 71–82%
OAK NCT02008227 phase III [91]	Atezolizumab vs docetaxel	Evaluate efficacy and safety of atezolizumab and docetaxel in patients with NSCLC after failure of platinum-containing chemotherapy	1225	<ul style="list-style-type: none"> • Primary efficacy analysis conducted on 850 of 1225 enrolled • OS: HR for atezolizumab vs docetaxel was 0.73; $P = .0003$ • Median PFS was 2.8 months vs 4.0 months • ORR = 13.6% vs 13.4% • OS for patients with PD-L1 expression of TC 1/2/3 or IC 1/2/3 was HR 0.74; $P = .0102$ for atezolizumab vs docetaxel • OS was improved regardless of PD-L1 expression (including no expression)

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; IC0 = no PD-L1 expression in tumor-infiltrating immune cells; NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PR = partial response; TCO = no PD-L1 expression in tumor cells; TPS = tumor proportion score; TRAE = treatment-related adverse event.

Table 2
Ongoing key trials of pembrolizumab in NSCLC.

Clinical trial	Purposes	N	Endpoints	Expected primary completion date	Estimated study completion
KEYNOTE-021 ^a NCT02039674 phase I/II	Determine safety, tolerability, and efficacy of pembrolizumab in combination with chemotherapy or immunotherapy in patients with unresectable or metastatic NSCLC	308	ORR , OS, PFS, and DOR	November 2016	October 2019
KEYNOTE-042 NCT02220894 phase III	Investigate efficacy of agent pembrolizumab for up to 35 treatments vs standard-of-care platinum-based chemotherapy in patients with PD-L1 expressing NSCLC	1240	OS and PFS	February 2018	February 2018
KEYNOTE-189 NCT02578680 phase III	Investigate efficacy of pembrolizumab in combination with platinum and pemetrexed vs platinum and pemetrexed therapy as first-line therapy in patients with non-squamous NSCLC	570	PFS , ORR, OS, and PFS by immune-related RECIST	September 2017	March 2019
KEYNOTE-407 NCT02775435 phase III	Investigate efficacy of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel vs carboplatin and paclitaxel/nab-paclitaxel therapy as first-line therapy in patients with squamous NSCLC	560	PFS, OS , and ORR	March 2018	August 2019

Abbreviations: DOR = duration of response; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors; TPS = tumor proportion score.

Endpoints in boldface are primary endpoints.

^a Pembrolizumab investigated as a combination drug.

(2.7–4.3), and 4.0 months (3.1–4.2) in the 2-mg/kg, 10-mg/kg, and docetaxel groups, respectively [49].

Pembrolizumab had a better safety profile than docetaxel, with fewer high-grade TRAEs, and the profile of the pembrolizumab treatment groups was as expected from the KEYNOTE-001 study [49]. TRAEs of grade ≥ 3 were reported in 43 of 339 patients (13%) and 55 of 343 patients (16%) in the pembrolizumab 2-mg/kg and 10-mg/kg groups, respectively, in comparison with 109 of 309 patients (35%) in the docetaxel group. TRAEs leading to study discontinuation occurred in 4%, 5%, and 10% of patients in the pembrolizumab 2-mg/kg, 10-mg/kg, and docetaxel groups, respectively. It was concluded that pembrolizumab 2 mg/kg and 10 mg/kg administered every 3 weeks conferred an OS benefit in all patients [49].

KEYNOTE-024

The ongoing KEYNOTE-024 study (NCT02142738) was designed to establish the efficacy and safety of pembrolizumab compared with standard of care (platinum-based chemotherapies) in patients with treatment-naïve, stage IV NSCLC whose tumors express PD-L1 on at least 50% of tumor cells. Patients were randomly assigned to receive either a 200-mg fixed-dose of pembrolizumab every 3 weeks or the investigator's choice of platinum-based combination chemotherapy. The primary endpoint was PFS, and secondary endpoints were ORR, OS, and safety [50]. Median PFS was 10.3 months (95% CI 6.7–not reached) versus 6.0 months (95% CI 4.2–6.2) for pembrolizumab compared with chemotherapy, respectively (HR 0.50; 95% CI 0.37–0.68; $P < .001$). The estimated 6-month OS rate was 80.2% in the pembrolizumab arm and 72.4% in the chemotherapy arm (HR 0.60; 95% CI 0.41–0.89; $P = .005$). ORR was 44.8% pembrolizumab arm and 27.8% in the chemotherapy arm. TRAEs occurred in 73.4% and 90.0% of patients in the pembrolizumab and chemotherapy arms, respectively [51]. These findings resulted in an independent data monitoring committee recommendation that the chemotherapy arm of the trial be discontinued and all patients in the trial receiving chemotherapy be offered the option to receive pembrolizumab [52]. Based on these results, the FDA, EMA, and Japanese PMDA approved pembrolizumab for first-line treatment of patients with metastatic NSCLC and high PD-L1 expression (TPS $\geq 50\%$) [40,41,45].

KEYNOTE-021

KEYNOTE-021 (NCT02039674) is an ongoing, multicohort, phase I/II study to assess the safety and antitumor activity of

first-line pembrolizumab in combination with chemotherapy or immunotherapy in unresectable or metastatic NSCLC [53]. An analysis of the randomized phase II pemetrexed/carboplatin cohort (cohort G) found an improved response rate with pembrolizumab 200 mg intravenously + pemetrexed and carboplatin compared with pemetrexed + carboplatin alone (ORR 55% versus 29%; $P = .0016$). TRAEs of any grade occurred in 93% of pembrolizumab + pemetrexed and carboplatin patients and in 90% of pemetrexed + carboplatin patients, including 39% and 26%, respectively, at grade ≥ 3 [53]. These data were submitted to the FDA in January 2017, resulting in the accelerated approval of pembrolizumab plus chemotherapy (pemetrexed plus carboplatin) for the first-line treatment of metastatic/advanced non-squamous NSCLC regardless of PD-L1 expression and with no *EGFR* or *ALK* genomic tumor aberrations [40].

Other PD-1 pathway inhibitors for advanced NSCLC

In addition to the nivolumab and atezolizumab studies (Table 1), several other PD-1 pathway inhibitors are currently under development as potential immunotherapies for patients with advanced or metastatic NSCLC. These include the anti-PD-L1 monoclonal antibodies durvalumab and avelumab; the anti-PD-1 monoclonal antibody PDR001; and the small-molecule PD-L1, PD-L2, and V-region IgG-containing suppressor of T-cell activation (VISTA) inhibitor CA-170.

Durvalumab is being explored as a treatment option in an open-label, phase III trial with or without another immune-checkpoint anti-CTLA4 inhibitor tremelimumab versus standard-of-care chemotherapy for treatment-naïve, *EGFR* and *ALK* wild-type, locally advanced or metastatic NSCLC patients (MYSTIC trial; NCT02453282) [54]. This followed results from the phase Ib trial in patients with locally advanced or metastatic NSCLC who were immunotherapy naïve but could have received other systemic treatments [55]. In this study, objective response occurred in six patients (23%) in the durvalumab 10–20 mg/kg every 2 or 4 weeks + tremelimumab 1 mg/kg cohort, and this included both patients who were PD-L1 negative ($n = 4$) and PD-L1 positive ($n = 2$), suggesting that PD-L1 status was not predictive of response to this combination regimen. Of the 26 patients in this dose cohort, 18 were treated with durvalumab 20 mg/kg every 4 weeks + tremelimumab 1 mg/kg, and this dose was recommended for the dose expansion phase [55]. The ongoing global, phase 3 PACIFIC trial is investigating the efficacy of durvalumab in patients with stage III unresectable NSCLC after concurrent chemoradiation and no evi-

dence of tumor progression (NCT02125461) [56]. Finally, durvalumab monotherapy and durvalumab with tremelimumab are also being compared with standard-of-care therapy in another open-label phase III trial of previously treated (\geq two prior chemotherapy regimens) patients with advanced or metastatic, PD-L1–positive (monotherapy) and PD-L1–negative (combination therapy) NSCLC (ARCTIC trial; NCT02352948) [57].

Avelumab yielded promising initial results as first-line monotherapy for advanced NSCLC in the open-label phase Ib JAVELIN solid tumor trial (NCT01772004). Preliminary findings (data cutoff, October 23, 2015) of the 75 patients who were followed up for a minimum of 3 months revealed an ORR of 18.7% (95% CI 10.6–29.3), with 1 complete response, 13 partial responses, and 34 patients with stable disease, for a disease control rate of 64.0% [58]. On the back of these findings, avelumab monotherapy is currently being compared with docetaxel as first-line therapy in patients with PD-L1–expressing NSCLC in the phase III JAVELIN Lung 100 trial (NCT02576574) [59], and as second-line therapy in the phase III JAVELIN Lung 200 trial (NCT02395172).

Role of PD-L1 as a predictive biomarker

Elevated PD-L1 expression is common in NSCLC. There are recent meta-analyses on the prevalence of PD-L1 expression in malignant tumors, as well as the predictive impact of PD-L1 expression on response to PD-L1 inhibitor treatment [60,61]. In one of the meta-analyses, which included 61 studies and 17 types of malignancy, the overall rate of PD-L1–positive tumors, as defined by the individual studies included, was found to be 44.5% (95% CI 37.5–51.6%). Furthermore, 51.7% (95% CI 33.1–70.3) of patients in 13 included studies on NSCLC were PD-L1 positive [60]. These observations, coupled with the approval of anti-PD-1 antibodies for the treatment of NSCLC, defined the need to evaluate the role of PD-L1 as a biomarker for treatment in specific treatment scenarios. A meta-analysis of seven studies (totaling 914 patients) showed that patients with PD-L1–positive tumors (tumor cell staining \geq 1%) had a significantly higher ORR than patients with PD-L1–negative tumors (odds ratio 2.44; 95% CI 1.61–3.68) [61]. Nivolumab and atezolizumab have been approved for treatment of patients with metastatic NSCLC after failure of platinum-based chemotherapy, regardless of PD-L1 expression [37,38], whereas pembrolizumab was approved specifically for use in patients with NSCLC tumors that express PD-L1 [40,41].

To date, four immunohistochemical PD-L1 assays have been approved for use in formalin-fixed NSCLC tissue: 22C3 pharmDx (Dako North America, Inc., Carpinteria, CA), approved as a companion diagnostic assay for pembrolizumab [62]; 28–8 pharmDx (Dako), approved as a complementary diagnostic assay for nivolumab [63]; SP263 (Ventana Medical Systems, a member of the Roche group, Tucson, AZ), approved as a companion diagnostic assay for pembrolizumab and as a complementary diagnostic assay for nivolumab [64]; and VENTANA PD-L1 (SP-142) (Ventana Medical Systems), approved as a complementary diagnostic assay for atezolizumab [65].

While the development of these assays will help toward elucidating the usefulness of PD-L1 expression as a biomarker of therapeutic efficacy for their respective drugs, differences in the antibodies used and in definitions of PD-L1 positivity between the assays render between-drug and between-study comparison extremely difficult. Aims to harmonize definitions and provide clarity on the analytic performance of PD-L1 assays has initiated cross-industry collaborations such as the Blueprint Project, a consortium of pharmaceutical companies, diagnostic companies, and academic institutions such as the International Association for the Study of Lung Cancer (IASCLC) [66,67]. The lack of validation

of any staining on cytological material makes the use of these biomarker assays difficult in daily practice, in which up to 40% of advanced disease diagnosis is made on such tumor samples [68].

The 22C3 pharmDx for use with pembrolizumab uses the 22C3 mouse antihuman PD-L1 antibody clone [62,69]. The level of positivity with this test is identified using TPS, which is defined as the percentage of viable tumor cells in a sample with \geq 1% membranous staining (at any intensity) and is described as no (TPS < 1%), low (TPS 1–49%), and high (TPS \geq 50%) expression [62].

The 28–8 pharmDx assay for use with nivolumab uses a 28–8 rabbit antihuman PD-L1 antibody clone, and positivity is stratified as \geq 1%, \geq 5%, and \geq 10% PD-L1 membrane staining at any intensity [63]. The assay was particularly precise and reproducible for staining at \geq 1% and \geq 5% [70].

The VENTANA PD-L1 SP-142 assay uses the rabbit monoclonal anti-PD-L1 clone SP-142. Unlike the previous two assays, the VENTANA assay evaluates PD-L1 expression on tumor cells and on tumor-infiltrating immune cells [65]. PD-L1 status is established by calculating either the percentage of tumor area occupied by PD-L1–expressing tumor-infiltrating immune cells (of any intensity; IC%) or the percentage of PD-L1–expressing tumor cells (of any intensity; % TC). PD-L1 expression was considered high at the cutoff values of \geq 10% for IC or \geq 50% for TC [65].

The VENTANA PD-L1 SP263 is a rabbit antihuman monoclonal primary antibody that is directed against the cytoplasmic region of human PD-L1 and has been designed to enable exploration of the expression of PD-L1 protein in tumor and immune cells in formalin-fixed, paraffin-embedded NSCLC and head and neck squamous cell carcinoma tissue [64,71,72]. A clinical cutoff of \geq 25% (of viable tumor cells with PD-L1 membrane staining of any intensity) is recommended, which discriminates responders from nonresponders [72].

PD-L1 expression as a biomarker

The role of PD-L1 expression as a biomarker for anti-PD-1 and anti-PD-L1 antibody treatment efficacy has been explored for pembrolizumab, nivolumab, and atezolizumab; the results are summarized in Table 3. KEYNOTE-001 was the first large clinical trial to demonstrate a positive correlation between PD-L1 expression and treatment response in NSCLC patients, and it included an endpoint to validate the 22C3 pharmDx assay by assessing the longitudinal outcomes of PFS and OS as related to PD-L1 expression [31,73,74]. The KEYNOTE-010 trial confirmed the findings of the KEYNOTE-001 trial, validating the use of PD-L1 expression as a diagnostic factor in combination with pembrolizumab. In that study, patients with TPS \geq 50% consistently displayed a survival benefit with pembrolizumab at both tested doses compared with the docetaxel group and the total population [49], although a post hoc analysis of efficacy found that pembrolizumab also prolonged survival over docetaxel in the subset of patients in KEYNOTE-010 with TPS 1–49% (Table 3) [75].

A similar relationship between PD-L1 expression and efficacy was seen in the phase II POPLAR study (NCT01903993) of atezolizumab versus docetaxel (Table 3) [35]. PD-L1 expression was prospectively assessed using the VENTANA SP-142 PD-L1 immunohistochemistry assay. Increase in improvement in OS was associated with an increase in PD-L1 expression [35].

The relationship between PD-L1 expression and efficacy of nivolumab in nonsquamous NSCLC was explored in the CheckMate057 trial (NCT01673867), using a retrospective analysis of prospectively collected pretreatment samples and the validated 28–8 pharmDx PD-L1 assay, and was stratified according to level of membranous PD-L1 staining (\geq 1%, \geq 5%, or \geq 10%) [76]. PD-L1 expression and clinical treatment response were strongly associated in a predictive context at all levels of PD-L1–positive staining

Table 3
Survival and response data for pembrolizumab, nivolumab, and atezolizumab stratified according to PD-L1 expression, measured using three different PD-L1 assays and with different definitions of PD-L1 expression.

Author	Assay	PD-L1 inhibitor/comparator	n (%)	PD-L1 cutoff for positivity	OS, months median (95% CI)	PFS, months median (95% CI)	ORR% (95% CI)
Garon [31]	22C3 pharmDx	Pembrolizumab	495 (100)	–	12 (9.3–14.7)	3.7 (2.9–4.1)	19.4 (16.0–23.2)
			73 (23.3) ^a	TPS ≥ 50%	NR (NR–NR)	6.4 (4.2–NR)	45.2 (33.5–57.3)
			103 (32.9) ^a	TPS 1–49%	10.6 (7.3–NR)	4.1 (2.3–4.4)	16.5 (9.9–25.1)
			28 (8.9) ^a	TPS < 1%	10.4 (5.8–NR)	4.0 (2.1–6.2)	10.7 (2.3–28.2)
Herbst [49] Garon [75]	22C3 pharmDx	Pembrolizumab 2 mg/kg	344 (100)	–	10.4 (9.4–11.9)	3.9 (3.1–4.1)	18 (14.1–22.5)
			139 (40.4) ^b	TPS ≥ 50%	14.9 (10.4–NR)	5.0 (4.0–6.5)	30 (22.7–38.8)
			205 (59.6) ^b	TPS 1–49%	9.4 (8.7–10.5)	3.1 (2.1–3.8)	10 (6–15)
			346 (100)	–	12.7 (10.0–17.3)	4.0 (2.7–4.3)	18 (14.5–23.0)
		Pembrolizumab 10 mg/kg	346 (100)	–	17.3 (11.8–NR)	5.2 (4.1–8.1)	29 (22.0–37.1)
			151 (43.6) ^c	TPS ≥ 50%	10.8 (8.9–13.3)	2.3 (2.1–4.0)	10 (6–15)
			195 (56.4) ^c	TPS 1–49%	8.5 (7.5–9.8)	4.0 (3.1–4.2)	9 (6.5–12.9)
			343 (100)	–	8.2 (6.4–10.7)	4.1 (3.6–4.3)	8 (4.1–13.4)
Docetaxel	191 (55.7) ^d	TPS 1–49%	8.6 (7.8–9.9)	3.9 (2.5–4.3)	10 (6–16)		
	343 (100)	–	8.5 (7.5–9.8)	4.0 (3.1–4.2)	9 (6.5–12.9)		
	152 (44.3) ^d	TPS ≥ 50%	8.2 (6.4–10.7)	4.1 (3.6–4.3)	8 (4.1–13.4)		
	191 (55.7) ^d	TPS 1–49%	8.6 (7.8–9.9)	3.9 (2.5–4.3)	10 (6–16)		
Borghaei [76]	28–8 pharmDx	Nivolumab	292 (100)	–	12.2 (9.7–15.0)	2.3 (2.2–3.3)	19 (15–24)
			123 (53.2) ^e	≥1%	17.7	4.2	31 (23–40)
			95 (41.1) ^e	≥5%	19.4	5.0	36 (26–46)
			86 (37.2) ^e	≥10%	19.9	5.0	37 (27–48)
		Docetaxel	290 (100)	–	9.4 (8.1–10.7)	4.2 (3.5–4.9)	12 (9–17)
			123 (54.9) ^f	≥1%	9.0	4.5	12 (7–19)
			86 (38.4) ^f	≥5%	8.1	3.8	13 (7–22)
			79 (35.3) ^f	≥10%	8.0	3.7	13 (6–22)
Fehrenbacher[35]	VENTANA SP-142	Atezolizumab	144 (100)	–	12.6 (9.7–16.4)	2.7 (2.0–4.1)	17 (11.0–23.8)
			24 (16.7)	TC3 or IC3	15.5 (9.8–NE)	7.8 (2.7–12.3)	37.5
			50 (34.7)	TC2/3 or IC2/3	15.1 (8.4–NE)	3.4 (1.4–6.9)	22.0
			93 (64.6)	TC1/2/3 or IC1/2/3	15.5 (11.0–NE)	2.8 (2.6–5.5)	18.3
			51 (35.4)	TC0 and IC0	9.7 (6.7–12.0)	1.7 (1.4–4.2)	7.8
		Docetaxel	143 (100)	–	9.7 (8.6–12.0)	3.0 (2.8–4.1)	15 (9.3–21.4)
			23 (16.1)	TC3 or IC3	11.1 (6.7–14.4)	3.9 (1.9–5.7)	13.0
			55 (38.5)	TC2/3 or IC2/3	7.4 (6.0–12.5)	2.8 (1.9–3.9)	14.5
			102 (71.3)	TC1/2/3 or IC1/2/3	9.2 (7.3–12.8)	3.0 (2.8–4.1)	16.7
			41 (28.7)	TC0 and IC0	9.7 (8.6–12.0)	4.1 (2.7–5.6)	9.8

Abbreviations: CI = confidence interval; NE = not estimable; NR = not reached; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; TC0, TC1, TC2, and TC3 = <1%, ≥1%, <5%, ≥5%, and <50%, ≥50% PD-L1-expressing tumor cells, respectively; IC0, IC1, IC2, and IC3 = <1%, ≥1% and <5%; ≥5% and <50%; and ≥50% PD-L1-expressing tumor-infiltrating immune cells, respectively.

^a N = 313 evaluable.

^b N = 344 evaluable.

^c N = 346 evaluable.

^d N = 343 evaluable.

^e N = 231 evaluable.

^f N = 224 evaluable.

and at all efficacy endpoints (Table 3). However, these findings must be interpreted with caution because of the retrospective nature of this analysis and the fact that tissue from only 78% of the study population was used for analysis [76].

In contrast with the immunotherapy agents, there seems to be no association between PD-L1 expression and prognosis in patients receiving platinum-based chemotherapy. A retrospective study of patients treated at a single center in Aarhus, Denmark from 2007 to 2012 included 204 treatment-naïve patients with stage IIIa, IIIb, or IV NSCLC who were treated with platinum-based chemotherapy [77]. No significant association was seen between PD-L1 expression and survival (log-rank test $P = .33$). The HR for patients with PD-L1 TPS 1–49% and ≥50% was 1.36 (95% CI 0.90–2.06) and 1.09 (95% CI 0.76–1.58), respectively, compared with the patients with TPS <1% [77]. These findings support the potential specificity of PD-L1 as a biomarker in conjunction with PD-1 pathway inhibitor therapies.

Challenges with the use of PD-L1 as a predictive biomarker

There remain several challenges regarding the use of PD-L1 assays [78], and further research is necessary to help understand the utility of PD-L1 as a predictive marker. In addition, the relative activity of anti-PD-1 or anti-PD-L1 checkpoint blockade in clinical studies will depend on the activity of the comparator chemother-

apy. In that regard, docetaxel is a toxic and poorly active standard as second-line therapy, allowing the positioning of some anti-PD-1 or anti-PD-L1 compounds as standards of care regardless of PD-L1 expression. In support of this, OS of atezolizumab and nivolumab in squamous cell carcinoma was superior to that of docetaxel in the subgroup of PD-L1-negative patients [79,80]. Nivolumab was equivalent in the nonsquamous subtype in this scenario [76]. Although the PD-L1-negative groups still show either noninferiority or some benefit of standard of care, the PD-L1 biomarker is associated with a better HR for benefit with increasing expression level. However, the comparison of anti-PD-1/PD-L1 compounds and frontline platinum-based chemotherapy requires PD-L1-related patient selection, as clearly shown through the positive KEYNOTE-024 trial (which required a PD-L1 tumor proportion score of ≥50%) [50] and negative CheckMate 26 trial (which required the lower cutoff of ≥5% PD-L1 tumor expression) [81].

There is currently no consensus on a threshold defining PD-L1 positivity, and multiple definitions are used, which hampers comparison of agents across studies. Trials thus far have selected thresholds most commonly at 1%, 5%, 25%, and/or 50%. Analysis of previous and current trials to determine which thresholds provided the greatest differences in response rates might provide a good indication of the most appropriate threshold for future use in diagnosis and treatment [48,78]. Efforts to see whether several thresholds can be measured using several assays have begun with the initiation of cross-industry collaborations such as the Blueprint

Project [66]. Regardless, the majority of trials to date have established that the higher the level of tumor PD-L1 expression, the more likely it will be that the patient will benefit from treatment with pembrolizumab [48,78].

The apparent significant, but not unequivocal, relationship between PD-L1 expression and responsiveness to PD-1/PD-L1 blockade [82] should be accepted with some caution because of the finding that some patients respond despite low PD-L1 expression [83] and the lack of a standardized method for evaluating that expression [82]. It has been suggested that the prediction of response to anti-PD-L1 treatment could be refined and maximized by the simultaneous evaluation of multiple relevant biomarkers [82].

The cell types used to determine PD-L1 positivity are not consistent among studies (e.g. tumor cells [84], tumor-infiltrating immune cells [31], stromal cells, and combinations thereof [85]), and the limited number of studies on PD-L1 expression in different cell types renders direct comparisons between studies challenging and potentially unreliable [78]. More extensive investigations into PD-L1 expression in various cell types and the corresponding observed response rates are warranted to determine the best standard, with the caveat that differences in tumor biology may result in different patterns of expression and associated response rates [48,78].

Another issue is the use of archival versus fresh tissue for PD-L1 expression, which varies between studies; the optimal tissue status in this context is a matter of debate. Some studies have argued that fresh (immediate, pretreatment) samples may not be obtainable, necessitating the use of archival (taken before first-line therapy) tissue. Because PD-L1 expression may change in response to systemic therapies, the use of new, recent samples before PD-L1 inhibitor administration might be more appropriate [78]. In contrast, an analysis of samples from the KEYNOTE-010 study revealed no difference in the PD-L1 expression predictive ability between archival and fresh test tissue [86].

The expression of PD-L1 may vary widely throughout the tumor so that the PD-L1 status of the biopsy sample might not accurately reflect the overall immunological status of the tumor [82]. In one study of 160 patients with operable NSCLC, PD-L1 expression in tumor cells was assessed in surgically resected and matched biopsy specimens, revealing a poor correlation between the two [87]. It was concluded that it would be advisable to take multiple biopsy samples from different areas of the tumor to enhance the validity of the results of immunohistochemical evaluations of PD-L1 [87], although putting this into practice would be difficult if not impossible for many patients, and there are no standards to determine this practice. However, in all studies showing an association between PD-L1 expression and benefit from therapy, the relationship between high PD-L1 expression and better outcome is largely maintained despite the potentially confounding effect of PD-L1 expression heterogeneity to which all of the samples would be subjected. The sometimes-conflicting findings regarding PD-L1 expression and its relationship with response rates warrant further investigation and refinement of the currently approved assays [77,78]. Validation of the PD-L1 assays in cytological material is ongoing and practically needed.

Other potential prognostic markers/biomarkers for pembrolizumab

Several other potential candidate biomarkers of response to pembrolizumab are either currently or planned subjects of investigation. CD8+ T-cell concentration and tumor mutational burden (including increased DNA repair pathway gene mutations), have been reported as possible predictive biomarkers in NSCLC in

response to pembrolizumab [48,88,89]. High expression of T-effector cell and interferon- γ -associated genes was associated with improved survival with atezolizumab in the phase II POPLAR study, and these gene signatures were not prognostic of survival in the docetaxel arm, suggesting their potential use as predictive biomarkers for atezolizumab benefit in NSCLC [35].

Other potential factors that have emerged in recent studies include smoking – which might be a surrogate of mutation burden – as well as specific tumor neoantigens, and these require further research to assess the validity of their use as prognostic factors in response to pembrolizumab therapy in NSCLC patients [36,78,88]. Several of these factors may emerge as possible biomarkers, most likely in combination with PD-L1 immunohistochemistry, but it remains to be seen whether such approaches are any better than the current standard. In the development of any biomarker, it is important to consider the practicalities of implementation on a routine basis.

Conclusions

The development of PD-L1 inhibitors for the treatment of patients with advanced NSCLC provides superior survival benefits in comparison with the more traditional treatments previously used. The anti-PD-1 inhibitor pembrolizumab is unique among the current immunotherapies because it has shown efficacy as a monotherapy when used as either second-line (PD-L1 expressing) or first-line (high PD-L1 expressing) therapy for patients with advanced NSCLC. In addition, initial results from randomized phase II cohort G of KEYNOTE-021 suggests that pembrolizumab combined with platinum doublet chemotherapy for first-line treatment in patients with NSCLC is tolerable and effective [53]. Multiple phase III studies are ongoing to fully evaluate the efficacy of pembrolizumab as first-line treatment; pembrolizumab as monotherapy in patients with NSCLC tumors that express PD-L1 is being evaluated in KEYNOTE-042 (NCT02220894). The combination of pembrolizumab with chemotherapy as first-line treatment in patients with NSCLC is being explored in two phase III studies: KEYNOTE-189 (NCT02578680) and KEYNOTE-407 (NCT02775435).

Biomarker selection of patients for anti-PD-1 and PD-L1 therapy has proven efficacy and clinical utility. PD-L1 immunohistochemistry is not a perfect biomarker, but no such single biomarker is known or likely, given the complexity of the immune response and its regulation. It remains to be seen whether addition of biomarkers accounting for tumor mutational burden (or a surrogate) and some assessment of tumor inflammation will enhance the accuracy of patient selection.

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Author contributions

Solange Peters: Collection, assembly, analysis, and interpretation of data. Drafting of manuscript and critically reviewing or revising the manuscript for important intellectual content.

Keith M Kerr: Conception, design or planning of the study. Drafting of manuscript and critically reviewing or revising the manuscript for important intellectual content.

Rolf Stahel: Conception, design or planning of the study, analysis of the data and interpreting the results. Critically reviewing or revising the manuscript for important intellectual content.

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References

- [1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136(5):E359–86.
- [2] Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol* 2015;16(1):36–46.
- [3] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346(2):92–8.
- [4] NCCN clinical practice guidelines in oncology: Non-small cell lung cancer version 5. 2017.
- [5] Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl 5):v1–27.
- [6] Gerber DE, Schiller JH. Maintenance chemotherapy for advanced non-small-cell lung cancer: new life for an old idea. *J Clin Oncol* 2013;31(8):1009–20.
- [7] Hirsh V. Systemic therapies in metastatic non-small-cell lung cancer with emphasis on targeted therapies: the rational approach. *Curr Oncol* 2010;17(2):13–23.
- [8] Alimta [package insert]. Indianapolis, IN: Eli Lilly and Company; 2016.
- [9] Taxotere [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2010.
- [10] Shepherd FA, Dancesy J, Rammlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18(10):2095–103.
- [11] Hanna N, Shepherd FA, Fossella FV, Pereira JR, de Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22(9):1589–97.
- [12] Haura EB. Treatment of advanced non-small-cell lung cancer: a review of current randomized clinical trials and an examination of emerging therapies. *Cancer Control* 2001;8(4):326–36.
- [13] Desai A, Menon SP, Dy GK. Alterations in genes other than EGFR/ALK/ROS1 in non-small cell lung cancer: trials and treatment options. *Cancer Biol Med* 2016;13(1):77–86.
- [14] Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M, Maiello MR, et al. Epidermal growth factor receptor (EGFR) signaling in cancer. *Gene* 2006;366(1):2–16.
- [15] Fazio N, Buzzoni R, Baudin E, Antonuzzo L, Hubner R, Lahner H, et al. A phase II study of BEZ235 in patients with everolimus-resistant, advanced pancreatic neuroendocrine tumours. *Anticancer Res* 2016;36(2):713–9.
- [16] Steuer CE, Ramalingam SS. ALK-positive non-small cell lung cancer: mechanisms of resistance and emerging treatment options. *Cancer* 2014;120(16):2392–402.
- [17] Wu J, Savoiji J, Liu D. Second- and third-generation ALK inhibitors for non-small cell lung cancer. *J Hematol Oncol* 2016;9:19.
- [18] Blackhall FH, Peters S, Bubendorf L, Dafni U, Kerr KM, Hager H, et al. Prevalence and clinical outcomes for patients with ALK-positive resected stage I to III adenocarcinoma: results from the European Thoracic Oncology Platform Lungscape Project. *J Clin Oncol* 2014;32(25):2780–7.
- [19] Wang S, Cang S, Liu D. Third-generation inhibitors targeting EGFR T790M mutation in advanced non-small cell lung cancer. *J Hematol Oncol* 2016;9:34.
- [20] Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015;372(18):1689–99.
- [21] Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19(8):2240–7.
- [22] Xalkori [summary of product characteristics]. Sandwick, UK: Pfizer Limited; 2016.
- [23] Xalkori [package insert]. New York, NY: Pfizer inc; 2017.
- [24] Alecensa [package insert]. South San Francisco, CA: Genentech, Inc.; 2016.
- [25] Zykadia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
- [26] Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;370(13):1189–97.
- [27] Ou SH, Ahn JS, De PL, Govindan R, Yang JC, Hughes B, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J Clin Oncol* 2016;34(7):661–8.
- [28] Caccese M, Ferrara R, Pilotto S, Carbognin L, Grizzi G, Calio A, et al. Current and developing therapies for the treatment of non-small cell lung cancer with ALK abnormalities: update and perspectives for clinical practice. *Expert Opin Pharmacother* 2016;17:2253–66.
- [29] Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017;377(9):829–38.
- [30] Rothschild SI. Targeted therapies in non-small cell lung cancer—beyond EGFR and ALK. *Cancers (Basel)* 2015;7(2):930–49.
- [31] Garon EB, Rizvi NA, Hui R, Leigh N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372(21):2018–28.
- [32] Scarpace SL. Metastatic squamous cell non-small-cell lung cancer (NSCLC): disrupting the drug treatment paradigm with immunotherapies. *Drugs Context* 2015;4:212289.
- [33] Armand P. Immune checkpoint blockade in hematologic malignancies. *Blood* 2015;125(22):3393–400.
- [34] Bustamante Alvarez JG, Gonzalez-Cao M, Karachaliou N, Santarpia M, Viteri S, Teixido C, et al. Advances in immunotherapy for treatment of lung cancer. *Cancer Biol Med* 2015;12(3):209–22.
- [35] Fehrenbacher L, Spira A, Ballinger M, Kowanzet M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387(10030):1837–46.
- [36] Dang TO, Ogunniyi A, Barbee MS, Drilon A. Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer. *Expert Rev Anticancer Ther* 2016;16(1):13–20.
- [37] Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc.; 2017.
- [38] Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
- [39] European Medicines Agency. Opdivo nivolumab. Committee for Medicinal Products for Human Use; 2016.
- [40] Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2017.
- [41] Keytruda [summary of product characteristics]. Hertfordshire, United Kingdom: Merck Sharp & Dohme, Limited; 2017.
- [42] Sharpe Merck, Corp Dohme. European Commission approves MSD's anti-PD-1 therapy, Keytruda (pembrolizumab), for both first-line and previously treated patients with advanced melanoma. Kenilworth, NJ: Merck Sharpe & Dohme; 2015.
- [43] US Food and Drug Administration. FDA approves Keytruda for advanced non-small cell lung cancer [approval letter]; 2014.
- [44] Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur R. FDA approval summary: pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death ligand 1. *Oncologist* 2016;21(5):643–50.
- [45] Merck & Co., Inc. KEYTRUDA® (pembrolizumab) approved as first anti-PD-1 therapy in Japan for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors express high levels of PD-L1 [press release]. Kenilworth, NJ: Merck & Co., Inc; 2016.
- [46] Gandhi L, Balmanoukian A, Hui R, Hamid O, Rizvi NA, Leigh N, et al. MK-3475 (anti-PD-1 monoclonal antibody) for non-small cell lung cancer: antitumor activity and association with tumor PD-L1 expression. *Cancer Res* 2014;74(19 suppl). Abstract CT105.
- [47] Hui R, Gandhi L, Costa EC, Felip E, Ahn M-J, Eder JP, et al. Long-term overall survival for patients with advanced NSCLC enrolled in the KEYNOTE-001 study of pembrolizumab (pembro). Presented at: ASCO Annual Meeting, June 3–7, 2016, Chicago, IL. Abstract 9026. *J Clin Oncol* 2016;34(suppl):9026.
- [48] Khoja L, Butler MO, Kang SP, Ebbinghaus S, Joshua AM. Pembrolizumab. *J Immunother Cancer* 2015;3:36.
- [49] Herbst RS, Baas P, Kim DW, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387(10027):1540–50.
- [50] Brahmer JR, Kim ES, Zhang J, Smith MM, Rangwala RA, O'Brien MER. KEYNOTE-024: Phase III trial of pembrolizumab (MK-3475) vs platinum-based chemotherapy as first-line therapy for patients with metastatic non-small cell lung cancer (NSCLC) that expresses programmed cell death ligand 1 (PD-L1). *J Clin Oncol* 2015;33(suppl). Abstract TPS8103.
- [51] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Czoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375(19):1823–33.
- [52] Business Wire. Merck's KEYTRUDA® (pembrolizumab) demonstrates superior progression-free and overall survival compared to chemotherapy as first-line treatment in patients with advanced non-small cell lung cancer [press

- release]. Published June 16, 2016. <http://www.businesswire.com/news/home/20160616005393/en/Merck%E2%80%99s-KEYTRUDA%C2%AE%C2%A0-pembrolizumab-Demonstrates-Superior-Progression-Free-Survival>.
- [53] Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016;17(11):1497–508.
- [54] Rizvi N, Barlesi F, Brahmer J, Felip E, Forde P, Garrasino M, et al. Phase III, randomized, open-label study of durvalumab (MEDI4736) in combination with tremelimumab or durvalumab alone versus platinum-based chemotherapy in first-line treatment of patients with advanced/metastatic NSCLC: MYSTIC. *J Immunother Cancer* 2015;3(suppl 2):P171.
- [55] Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumor activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. *Lancet Oncol* 2016;17(3):299–308.
- [56] Cho BC, Kim JH, Villegas A, Frusch N, Murakami S, Shi K, et al. Phase 3, double-blind, placebo-controlled study of MEDI4736 after chemoradiation in stage III, locally advanced, unresectable NSCLC (PACIFIC). *J Thorac Oncol* 2015;10(9 suppl 2):S668.
- [57] Planchard D, Yokoi T, McCleod MJ, Fischer JR, Kim YC, Ballas M, et al. A phase III study of curvalumab (MEDI4736) with or without tremelimumab for previously treated patients with advanced NSCLC: rationale and protocol design of the ARCTIC study. *Clin Lung Cancer* 2016;17(3):232–6.
- [58] Verschraegen CF, Chen F, Spigel DR, Iannotti N, McClay EF, Redfern CH, et al. Avelumab (MSB0010718C; anti-PD-L1) as a first-line treatment for patients with advanced NSCLC from the JAVELIN solid tumor phase 1b trial: safety, clinical activity, and PD-L1 expression. *J Clin Oncol* 2016;34(suppl). Abstract 9036.
- [59] Reck M, DeGreen HP, Rose AL, Pavlakis N, Derjcke SM, Radic J, et al. Avelumab (MSB0010718C; anti-PD-L1) vs platinum-based doublet as first-line treatment for metastatic or recurrent PD-L1-positive non-small-cell lung cancer: The phase 3 JAVELIN Lung 100 trial. *J Clin Oncol* 2016;34(suppl). Abstract TPS9105.
- [60] Lin Z, Xu Y, Zhang Y, He Q, Zhang J, He J, et al. The prevalence and clinicopathological features of programmed death-ligand 1 (PD-L1) expression: a pooled analysis of literatures. *Oncotarget* 2016;7(12):15033–46.
- [61] Passiglia F, Bronte G, Bazan V, Natoli C, Rizzo S, Galvano A, et al. PD-L1 expression as predictive biomarker in patients with NSCLC: a pooled analysis. *Oncotarget* 2016;7(15):19738–47.
- [62] Dako North America, Inc. PD-L1 IHC 22C3 pharmDx. Dako North America Inc: Carpinteria, CA; 2015.
- [63] Dako Agilent Pathology Solutions. PD-L1 IHC 28–8 pharmDx: Interpretation Manual—Non-squamous non-small cell lung cancer (ROW Version); 2016.
- [64] Ventana Medical Systems Inc. VENTANA PD-L1 (SP263) Assay; 2017.
- [65] Roche Group Media Relations. Roche announces FDA approval for VENTANA PD-L1 (SP142) Assay to support immunotherapy treatment decisions in lung cancer [press release]. Published October 27; 2016. <<http://www.prnewswire.com/news-releases/roche-announces-fda-approval-for-ventana-pd-l1-sp142-assay-to-support-immunotherapy-treatment-decisions-in-lung-cancer-300352191.html>>.
- [66] Hirsch FR, Averbuch S, Emami T, Walker J, Williams A, Stanforth D, et al. The Blueprint Project: harmonizing companion diagnostics across a class of targeted therapies. New Orleans, LA; 2016.
- [67] Averbuch S, Emancipator K, McCaffery I, McElhinny A, Stanforth D, Walker J, et al. A blueprint proposal for companion diagnostic comparability. <<https://www.fda.gov/downloads/medicaldevices/newsevents/workshopsconferences/ucm439440.pdf>> [accessed July 20, 2017].
- [68] Kerr KM, Bubendorf L, Edelman MJ, Marchetti A, Mok T, Novello S, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol* 2014;25(9):1681–90.
- [69] Dolled-Filhart M, Locke D, Murphy T, Lynch F, Yearley JH, Frisman D, et al. Development of a prototype immunohistochemistry assay to measure programmed death ligand-1 expression in tumor tissue. *Arch Pathol Lab Med* 2016;140(11):1259–66.
- [70] Phillips T, Simmons P, Inzunza HD, Cogswell J, Novotny Jr J, Taylor C, et al. Development of an automated PD-L1 immunohistochemistry (IHC) assay for non-small cell lung cancer. *Appl Immunohistochem Mol Morphol* 2015;23(8):541–9.
- [71] Liu D, Wang S, Bindeman W. Clinical applications of PD-L1 bioassays for cancer immunotherapy. *J Hematol Oncol* 2017;10:110.
- [72] Rebelatto MC, Midha A, Mistry A, Sabalos C, Schechter N, Li X, et al. Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. *Diagn Pathol* 2016;11(1):95.
- [73] Roach C, Zhang N, Corigliano E, Jansson M, Toland G, Ponto G, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. *Appl Immunohistochem Mol Morphol* 2016;24(6):392–7.
- [74] Dolled-Filhart M, Roach C, Toland G, Stanforth D, Jansson M, Lubiniecki GM, et al. Development of a companion diagnostic for pembrolizumab in non-small cell lung cancer using immunohistochemistry for programmed death ligand-1. *Arch Pathol Lab Med* 2016 [Epub ahead of print].
- [75] Garon EB, Herbst RS, Kim D-W, Felip E, Perez-Gracia JL, Han J-Y, et al. Pembrolizumab vs docetaxel for previously treated advanced NSCLC with a PD-L1 tumor proportion score (TPS) 1%–49%: results from KEYNOTE-010. Presented at: ASCO Annual Meeting, June 3–7, 2016, Chicago, IL. Abstract 9024.
- [76] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373(17):1627–39.
- [77] Sorensen SF, Zhou W, Dolled-Filhart M, Georgsen JB, Wang Z, Emancipator K, et al. PD-L1 expression and survival among patients with advanced non-small cell lung cancer treated with chemotherapy. *Transl Oncol* 2016;9(1):64–9.
- [78] Karim S, Leighl N. Pembrolizumab for the treatment of thoracic malignancies: current landscape and future directions. *Future Oncol* 2016;12(1):9–23.
- [79] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubska E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373(2):123–35.
- [80] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389(10066):255–65.
- [81] Socinski M, Horn L, Steins M, Ciuleanu TE, Ready N, Nair RG, et al. A phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage iv/recurrent programmed death ligand 1 (PD-L1)-positive NSCLC. *Ann Oncol* 2016;27(suppl 6) [Abstract LBA7-PR].
- [82] Ilie M, Hofman V, Dietel M, Soria JC, Hofman P. Assessment of the PD-L1 status by immunohistochemistry: challenges and perspectives for therapeutic strategies in lung cancer patients. *Virchows Arch* 2016;468(5):511–25.
- [83] Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol* 2016;39(1):98–106.
- [84] Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Ellassais-Schaap J, Beeram M, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res* 2015;21(19):4286–93.
- [85] Seiwert TY, Burtress B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 2016;17(7):956–65.
- [86] Herbst RS, Baas P, Perez-Garcia JL, Felip E, Kim DW, Han JY, et al. Archival vs new tumor samples for assessing PD-L1 expression in the KEYNOTE-010 study of pembrolizumab (pembro) vs docetaxel (doce) for previously treated advanced NSCLC. *J Clin Oncol* 2016;34(suppl). Abstract 3030.
- [87] Ilie M, Long-Mira E, Bence C, Butori C, Lassalle S, Bouhler L, et al. Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies. *Ann Oncol* 2016;27(1):147–53.
- [88] Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;348(6230):124–8.
- [89] Peters S, Creelan B, Hellman MD, Socinski MA, Reck M, Bhagavatheswaran P, et al. Impact of tumor mutation burden on the efficacy of first-line nivolumab in stage iv or recurrent non-small cell lung cancer: an exploratory analysis of CheckMate 026. Presented at: AACR Annual Meeting 2017, Washington, DC, April 1–5, 2017.
- [90] Besse B, Johnson ML, Janne PA, Garissino M, Eberhardt WEE, Peters S, et al. Phase II single arm trial (BIRCH) of atezolizumab as first line or subsequent therapy for locally advanced or metastatic PD-L1 selected NSCLC. *Eur J Cancer* 2015;51(suppl 3):S717–718.
- [91] Barlesi F, Von Pawel J, Kowalski D, Leach J, Gandara D, Chen DS, et al. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC. *Ann Oncol* 2016;27(Suppl. 6) [Abstract LBA44-PR].