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Targeting the PD-1/PD-L1 axis in the treatment of lung cancer

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Abstract: In recent years major advances in the field of molecular profiling of non-small cell lung cancer led to the identification of targetable driver mutations and revolutionized the treatment of specific patient subsets. However, the majority of NSCLC tumors do not harbor these genomic events. On the other hand, current studies have confirmed an expanding role for immunotherapy in lung cancer and new agents, such as inhibitors of the programmed cell death-1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis have been introduced in the treatment armamentarium. The monoclonal antibodies nivolumab and pembrolizumab targeting PD-1 resulted in superior survival when compared to standard second line chemotherapy within the context of randomized trials and received regulatory approval. Moreover, several other anti-PD-L1 antibodies have demonstrated encouraging preliminary efficacy and multiple clinical trials in various settings during the disease trajectory are currently underway. Early immunotherapy trials have also illustrated the potential of PD-1 blockade in small cell lung cancer treatment, a disease for which major advances in systemic therapy are lacking. The currently available clinical data on PD-1/PD-L1 inhibition in lung cancer are summarized in this review.

Keywords: *NSCLC • PD-1 • PD-L1 • Nivolumab • Pembrolizumab*

1. Introduction

Lung cancer is the leading cause of cancer-related deaths in men and women [1]. Almost 80% of bronchogenic carcinomas are of the non-small cell lung cancer (NSCLC) subtype and approximately half of the patients with newly diagnosed NSCLC present with metastatic disease. The median overall survival (OS) for these patients is approximately 10 months and the 5-year survival rates are less than 1% [2].

The identification of several driver mutations in NSCLC, the recognition of the phenomenon of 'tumour addiction' to these mutations and the development of potent targeted agents has clearly improved outcomes in a small subset of patients. These targets include, but are not limited to, the epidermal growth factor receptor (EGFR) [3-5], the echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase fusion gene (EML4-ALK) [6] and the ROS1 proto-oncogene receptor tyrosine kinase (ROS1) [**7**]. However, despite impressive response rates, the development of acquired resistance to these targeted agents is inevitable. Consequently, for the vast majority palliative cytotoxic chemotherapy remains the only available treatment option and although it offers symptom palliation and a modest prolongation of survival, results are far from optimal, underscoring the need for more effective treatment strategies.

By contrast, little progress has been made in the treatment of extensive stage small cell lung cancer (SCLC) during the past two decades. Various strategies applied in order to improve upon the results of the platinum–etoposide combination, such as combining different agents, increasing dose density or intensity or adding more drugs, have failed [8-10]. Today, chemotherapy remains the cornerstone of the management of SCLC, with no targeted therapies currently approved either for the first line or the relapsed setting.

2. Principles of cancer immunotherapy – the role of PD-1

Cancer immunotherapy has markedly different goals compared to traditional cytotoxic chemotherapy,

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which include the reversal of tumour-induced immune tolerance, the promotion of the recognition of cancer as a foreign invader and finally the stimulation of immune response. Although early attempts towards cancer immunotherapy can be traced as far back as the late 19th century, in recent years the exponential advances in the understanding of tumour–host interplay have led to important breakthroughs in the treatment of solid tumours, especially melanoma and NSCLC.

The recognition by the T-cells of antigens bound to specific major histocompatibility complex (MHC) molecules and presented by the antigen-presenting cells (APCs), is the decisive first step in the process of immune recognition. This recognition is regulated by several inhibitory molecules such as the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed death protein 1 (PD-1), termed immune checkpoints. PD-1 is expressed on the surface of T cells, NK cells, macrophages and B cells. When bound by its ligands, PD-L1 and PD-L2, PD-1 inhibits the activation of T cells and downregulates the production of certain cytokines such as IL-2, IL-10 and IFN-γ [11]. Conceivably, blockade of the PD-1/PD-L1 axis promotes the anti-tumour immune response and monoclonal antibodies directed against these molecules have demonstrated clinically relevant activity in multiple solid tumours.

Before reviewing the available data concerning the role of PD-1 and PD-L1 inhibitors in the treatment of lung cancer, it is worth noting that the response evaluation criteria (RECIST) in solid tumours may not be appropriate to adequately assess the effectiveness of cancer immunotherapy. Delayed response kinetics are frequently observed, whereas, a flare response, or a transient worsening of the disease may be encountered due to immune infiltration of the tumour or to early disease progression before the treatment effect occurs. Moreover, prolonged disease stabilisation, which is considered as a clinically meaningful therapeutic effect, is often recognised. For these reasons, immune-related response criteria have been proposed that take into account the particularities of immune response patterns observed with immunotherapeutic agents [12].

3. Antibodies targeting PD-1: nivolumab and pembrolizumab

3.1 Nivolumab

Nivolumab is an IgG4 anti-PD-1 monoclonal antibody that, as of January 2016, has received regulatory approval by the United States Food and Drug Administration (FDA) for metastatic melanoma either alone or in combination with ipilimumab for the second line treatment of advanced NSCLC and for pretreated advanced renal cancer [13]. The European Medicines Agency (EMA) has approved the agent for advanced melanoma and advanced squamous NSCLC after prior chemotherapy [14]. Although multiple regimens have been evaluated in clinical trials, the approved dose is 3 mg/kg, administered intravenously every 2 weeks.

The activity of nivolumab in advanced NSCLC was first demonstrated in a phase I trial, where in a cohort of 129 pretreated patients, of whom more than half had received at least three prior systemic therapies, were treated for up to 2 years. The response rate (RR), according to RECIST criteria, was 17%, an additional 5% achieved unconventional immune responses and 10% long-lasting disease stabilisation. The one- and three-year survival rates for the cohort of patients treated with 3 mg/kg every 2 weeks were 56% and 27%, respectively, unprecedented for patients with advanced refractory disease. Moreover, response rates did not differ between patients with squamous and non-squamous NSCLC and between PD-L1 positive and negative tumours, using the cut-off of 5% of positive cells by immunohistochemistry (IHC). Treatment was well tolerated, with only 14% of patients experiencing grade 3 or 4 adverse events [15]. In the follow-up CheckMate 063, a single-arm phase II trial, 117 patients with advanced NSCLC who had received at least two prior lines of therapy, received nivolumab 3 mg/kg every 2 weeks; treatment continuation after disease progression was allowed. Overall survival (OS) was 8.2 months and the objective response rate was 14.5% according to RECIST criteria. Grade 3 and 4 treatment-related adverse events were observed in 17% of the patients including fatigue (4%), pneumonitis (3%) and diarrhea (3%) [16].

The activity of nivolumab in the second line setting for both squamous and non-squamous NSCLC has been clearly demonstrated in two phase III trials. In CheckMate 017, 272 patients with advanced squamous NSCLC, who had progressed after initial treatment with a platinum based doublet, were randomised to receive either nivolumab, 3 mg/kg every 2 weeks or docetaxel, 75 mg/m^2 every 21 days, until disease progression. The primary endpoint of the trial was overall survival. After a minimum follow-up of 11 months, median OS was superior for the nivolumab arm compared to the docetaxel arm [9.2 months versus 6.0 months (HR 0.59; 95% CI, 0.44 to 0.79; P<0.001)]. The response and one-year survival rates were 20% versus 9% (P=0.008) and 42% versus 24% (P=0.008) for nivolumab versus docetaxel, respectively. The median progression-free survival (PFS) was 3.5 months with nivolumab versus

2.8 months with docetaxel (*P*<0.001). Various cut-offs of PD-L1 expression were evaluated and were found to be neither prognostic nor predictive for benefit from nivolumab. Nivolumab was better tolerated compared to chemotherapy: grade 3 or 4 toxicities occurred in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group. Quality of life and relief of symptom burden also clearly favoured the nivolumab arm [17]. In the similarly designed CheckMate 057, 587 patients with advanced non-squamous NSCLC that had progressed after first-line platinum based doublet, were randomised to receive either nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m^2 every 21 days, until disease progression. The primary endpoint of the trial was overall survival. After a minimum follow-up of 13.2 months, median OS was 12.2 months (95% CI, 9.7 to 15.0) for the nivolumab group and 9.4 months (95% CI, 8.1 to 10.7) for the docetaxel group (HR 0.73; 96% CI, 0.59 to 0.89; P=0.002). The one-year survival rates were 51% with nivolumab versus 39% with docetaxel. The RR according to RECIST 1.1 was 19% with nivolumab versus 12% with docetaxel (*P*=0.02). Although progression-free survival did not favour nivolumab over docetaxel (median, 2.3 months and 4.2 months, respectively), the rate of progression-free survival at 1 year was higher with nivolumab (19% vs 8%). Remarkably, the median duration of response was 17.2 months for nivolumab and 5.6 months for docetaxel. Various levels of PD-L1 expression were evaluated (1%, 5% and 10%), which revealed a predictive association between PD-L1 expression and benefit from anti–PD-1 treatment. However, in PD-L1 positive patients, survival was significantly longer in the nivolumab compared to docetaxel, regardless of the level of PD-L1 positivity. In accordance with CheckMate 017, treatment-related adverse events of grade 3 or 4 were reported in 10% of the patients in the nivolumab group, as compared with 54% of those in the docetaxel group [18]. Interestingly, according to data presented in the 2015 European Cancer Congress (ECC 2015), the likelihood of obtaining a response from treatment with nivolumab was not affected by the presence of brain metastases, progression-free interval from previous treatment, gender, age or prior maintenance treatment; however, never-smokers and patients whose tumours harboured activating EGFR mutations had lower response rates [19]. In short, these two phase III trials have established nivolumab as a new standard of care in the second-line treatment of advanced NSCLC due to the clear benefit in overall survival compared to docetaxel combined with a more favourable safety profile.

Nivolumab has also been evaluated in treatment naïve patients. In the multi-arm phase I trial, CheckMate 012, the safety and tolerability of nivolumab is evaluated in the first-line either as a monotherapy or in combination with other agents, including ipilimumab. Among 52 patients that received nivolumab monotherapy, median OS was 98.3 weeks whereas response rates were higher in patients with PD-L1 positive tumours [31% versus 10% (IHC cut-off 5%)] [20**].** Moreover, nivolumab has been combined with platinum-based doublet chemotherapy [21], or ipilimumab [22] or erlotinib in EGFR-mutated NSCLC patients [23]; results have only been presented in abstract form. In the CheckMate 012 trial, four different dosing schedules of the combination of nivolumab with ipilimumab, proven effective in metastatic melanoma albeit at the cost of increased toxicity [24], were administered in 148 treatment-naïve patients with advanced NSCLC. The best results were noted at arm C and D, with nivolumab at 3 mg/kg every 2 weeks and ipilimumab at 1 mg/kg every 12 (*N*=38) or 6 weeks (*N* = 39). ORR was 39% and 31% and 24-week PFS rates were 74% and 65%, respectively. The safety profile was consistent with previous studies of the combination, and the discontinuation rate associated with adverse events was similar to the rates observed with nivolumab monotherapy [22**]**. Ongoing trials of nivolumab and other immune checkpoint inhibitors are summarised in Table 1.

3.2 Pembrolizumab

Pembrolizumab is an IgG4 monoclonal antibody that targets PD-1. As of January 2016, it has received regulatory approval at the dose of 2 mg/kg every 3 weeks by the FDA, for use in metastatic melanoma after disease progression on ipilimumab and in PD-L1 positive NSCLC that progressed after platinum based chemotherapy and by the EMA for use in advanced melanoma [25, 26]. The regulatory approval for NSCLC was based on a large dose expansion phase I trial, KEYNOTE-001, where 495 pretreated NSCLC patients received pembrolizumab at different doses and schedules. The median OS for the entire cohort was 12.0 months, the median PFS 3.7 months and the RR 19.4%, with a median duration of response of 12.5 months. The cut-off for PD-L1 positivity according to IHC was 50% of positive tumour cells; in this patient subset, RR was 45.2% (43.9% for previously treated patients and 50% for untreated patients), median PFS 6.3 months and median OS had not yet been reached. It should be noted that among 824 screened samples, the prevalence of 50% PD-L1 positivity was 23.2%, whereas 39.2% of samples had less than 1% PD-L1 positive tumour cells. Treatment with pembrolizumab was well tolerated, with

Table 1. Ongoing phase III trials of anti-PD-1/PD-L1 agents and combinations in Non-Small Cell Lung Cancer and Small Cell Lung Cancer.

Agent	Clinical Setting	Comparison	Clinicaltrials.gov Identifier
Nivolumab			
	First line, any NSCLC histology	Vs platinum doublet (physician's choice)	NCT02041533
	First line, any NSCLC histology	4 arms: nivolumab vs nivolumab/ipilimumab vs nivolumab/chemotherapy vs chemotherapy (platinum based doublet, physician's choice)	NCT02477826
	Second line NSCLC after platinum based doublet	Vs docetaxel	NCT02613507
	Adjuvant treatment NSCLC after resection and chemotherapy	Vs placebo	NCT02595944
	Relapsed SCLC	Vs topotecan or amrubicin	NCT02481830
	Extensive SCLC, maintenance after first line treatment	nivolumab vs nivolumab/ipilimumab vs placebo	NCT02538666
Pembrolizumab			
	Adjuvant treatment NSCLC after resection with or without chemotherapy	Vs placebo	NCT02504372
	First line, any NSCLC histology, PD-L1 positive	Vs platinum based doublet chemotherapy	NCT02220894
	First line, any NSCLC histology	Vs platinum based doublet chemotherapy	NCT02142738
	First line, any NSCLC histology	Platinum/pemetrexed, with or without pembrolizumab	NCT02578680
Atezolizumab			
	First line, non-squamous NSCLC	Platinum/pemetrexed, with or without atezolizumab	NCT02657434
	First line, squamous NSCLC	Carboplatin/taxane with or without atezolizumab	NCT02367794
	First line, PD-L1 positive squamous NSCLC	Vs platinum/gemcitabine	NCT02409355
	First line, PD-L1 positive non-squamous NSCLC	Vs platinum/pemetrexed	NCT02409342
	First line, non-squamous NSCLC	3 arms: paclitaxel/carboplatin/atezolizumab vs paclitaxel/carboplatin/bevacizumab vs paclitaxel/carboplatin/bevacizumab/atezolizumab	NCT02366143
	First line, non-squamous NSCLC	Carboplatin/nab-paclitaxel with or without atezolizumab	NCT02367781
	Second line NSCLC after platinum based doublet	Vs docetaxel	NCT02008227
	Adjuvant treatment NSCLC after resection and chemotherapy	Vs placebo	NCT02486718
Durvalumab			
	First line, any NSCLC histology	Durvalumab vs durvalumab/tremelimumab vs platinum based doublet	NCT02453282
	Stage III NSCLC following chemoradiotherapy	Vs placebo	NCT02125461
	Adjuvant treatment NSCLC after resection and chemotherapy	Vs placebo	NCT02273375
	Third line NSCLC	Durvalumab vs durvalumab/tremelimumab vs monotherapy (gemcitabine, vinorelbine or erlotinib)	NCT02352948

the most common side effects being fatigue, pruritus and decreased appetite [27]. In a subgroup analysis from the KEYNOTE-001 trial presented at the 2015 World Conference on Lung Cancer (WCLC 2015), PD-L1 positivity and smoking status were found to be independently correlated with an increased likelihood of response. Moreover, patients whose tumours harboured activating EGFR mutations achieved a lower response rate, independently of PD-L1 positivity; on the contrary, KRAS mutation status did not affect response rates. Finally, although patients with squamous NSCLC had numerically higher response rates and PFS compared

Table 2. Published trials in full form of PD-1 inhibitors.

Agent	Reference	Phase	N	Comparison/ Setting	Response Rate	PFS (months)	OS (months)	Comments
Nivolumab								
	Gettinger et al [15]	1	129	N/A / Heavily pretreated	17%	2.3	9.9	
	Rizvi et al [16]	2	117	N/A / Heavily pretreated	14,5%	1.9	8.2	
	Brahmer et al [17]	3	272	Docetaxel / 2nd line squamous	20% vs 8% (P=0.008)	3.5 vs 2.8 (P<0.001)	9.2 vs 6.0 (P<0.001)	
	Borghaei et al [18]	3	587	Docetaxel / 2nd line non-squamous	19% vs 12% (P=0.02)	2.3 vs 4.2 (NS)	12.1 vs 9.4 (P=0.002)	
Pembrolizumab	Garon et al [27]	1	495	N/A / Heavily pretreated	19,4%	3.7	12.0	
	Herbst et al [29]	2/3	1043	Docetaxel / 2nd line PD-L1≥1%	18% vs 9% (P=0.0002)	4.0 vs 4.0 (NS)	12.7 vs 8.5 (P<0.0001)	10 mg/kg arm vs docetaxel
	Herbst et al [29]	2/3	1043	Docetaxel / 2nd line PD-L1≥1%	18% vs 9% (P=0.0005)	3.9 vs 4.0 (NS)	10.4 vs 8.5 (P=0.0008)	2 mg/kg arm vs docetaxel

to non-squamous NSCLC, none of the patients with squamous histology and <1% PD-L1 positivity derived any benefit from pembrolizumab [28].

In the recently published phase II/III KEYNOTE-010 trial, 1043 patients who had progressed following a platinum doublet and expressed PD-L1 on more than 1% of tumour cells, were randomised to receive second-line pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg or docetaxel 75 mg/m^2, every 21 days. OS was 10.4 and 12.7 months with pembrolizumab (at 2 mg/kg and 10 mg/kg, respectively) and 8.5 months with docetaxel [hazard ratio (HR) 0.71, 95% CI 0.58–0.88; (*p*=0.0008) for pembrolizumab 2 mg/kg and 0.61, 0.49-0.75; (*p*<0.0001) for 10 mg/kg]. Median PFS was 3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg and and 4.0 months with docetaxel, with no significant difference between the three arms. Among 'strongly PD-L1–positive' patients, defined as those expressing PD-L1 on ≥50% of their tumour cells, both OS and PFS was significantly longer for both doses of pembrolizumab versus docetaxel. Grades 3 to 5 treatment-related adverse events were less common with pembrolizumab than with docetaxel (13% at the low dose arm, 16% at the high dose arm, and 35% at the chemotherapy arm) [29].

The development of brain metastases is a common event in advanced NSCLC and a harbinger of poor prognosis [30]. Although widely used, whole brain radiation therapy (WBRT) failed to improve outcomes over optimal supportive care in the randomised QUARTZ trial [31]. In a small phase II trial, 18 patients with NSCLC and progressive brain disease were assessed for response after treatment with pembrolizumab at the dose of 10 mg/kg every 2 weeks. Most patients had received at least one prior systemic treatment and approximately half of the patients had received local treatment for brain lesions (surgery, stereotactic radiotherapy or WBRT). The response rates for brain and systemic disease were similar at 33% and the central nervous system responses were durable, consistent with previous reports of PD-1 blockade [32]. The results of the full publication of clinical trials of PD-1 antibodies are summarised in Table 2.

4. Antibodies targeting PD-L1: atezolizumab, durvalumab and BMS-936559

PD-L1 production at the tumour level is considered to be the main contributing factor for PD-1 mediated immune evasion. Since PD-L2 is mainly expressed in the normal tissue, it is thought that specific anti-PD-L1 antibodies could provide comparable clinical benefits to PD-1 blockade but with decreased toxicity, especially regarding autoimmune lung injury.

Atezolizumab (formerly MPDL3280A) is an IgG1 fully humanised antibody that targets PD-L1 and is

currently under evaluation in multiple solid tumours. Regarding NSCLC, the results of two large phase II trials were recently presented at the ECC 2015. BIRCH trial enrolled 667 patients presenting high PD-L1 expression in tumour cells (TC) and/or tumour-infiltrating immune cells (IC). Patients received atezolizumab at a fixed dose of 1200 mg every 3 weeks in the first or subsequent line setting. The ORR was 19% in cohort 1 (first line) and 17% in cohorts 2 (second line) and 3 (third line and beyond) among patients with TC2/3 or IC2/3 expression. At a median follow-up of 8.8, 7.9 and 8.6 months, median OS was 14 months, not reached (NR), and NR, across cohorts 1, 2, and 3, respectively. High levels of PD-L1 were predictive for benefit from atezolizumab: in cohorts 1, 2, 3 and 6-month survival rates were 76%, 75%, and 71%, respectively, among patients with TC2/3 or IC 2/3 expression levels and 79%, 82%, and 80% for those with TC3 or IC3 expression levels. Similarly, 6-month PFS rates were 29%, 39% and 31% among patients with TC2/3 and IC 2/3 expression levels and 48%, 46% and 34% for TC3 or IC3 in cohorts 1, 2 and 3, respectively. The safety profile was consistent with that demonstrated in other studies; grade 3/4 treatment-related adverse events occurred in 11% of patients and 6% discontinued treatment because of toxicities [33]. In a randomised phase II trial, POPLAR, standard second line docetaxel was compared to atezolizumab in 287 previously treated patients with NSCLC. ORR was 15% with both treatments, median OS was 12.6 and 9.7 months and the median PFS was 2.7 and 3.0 months, for atezolizumab and docetaxel, respectively. However, among patients with high PD-L1 expression levels (TC/IC3), the median PFS was 7.8 and 3.9 months for atezolizumab and docetaxel, and the ORR was 38% and 13%, respectively. In contrast, in patients without PD-L1 expression (TC/IC 0), no difference in OS, PFS or ORR was observed between the two groups [34]. Finally, in a phase I trial, atezolizumab was combined with various platinum-based chemotherapy doublets and results were presented at the WCLC 2015. Out of 41 patients evaluable for response assessment, the ORR was 63.4%; patients receiving carboplatin, pemetrexed and atezolizumab had an ORR of 77%. Myelotoxicity, especially neutropenia, was the most common grade 3/4 adverse event [35].

Durvalumab (formerly MEDI4736), an IgG1 antibody, and BMS-936559, an IgG4 antibody, are in earlier stages of development. Results from phase I trials indicate that these agents bear activity comparable to other PD-1/PD-L1 inhibitors in patients with advanced NSCLC [36, 37]. Durvalumab has also been combined with tremelimumab, a CTLA-4 inhibitor, in previously treated NSCLC patients. ORR across various dosing cohorts was 25%; patients with both PD-L1 positive and negative tumours experienced objective responses; however, toxicity was substantial with 42% of patients experiencing a grade 3 or 4 adverse event and 16% discontinuing treatment due to adverse events [38]. Notably, durvalumab is being studied in multiple phase III trials in NSCLC which are summarised in Table 1.

5. PD-1/PD-L1 inhibition in NSCLC: Current controversies and future directions

Available efficacy data clearly indicate that PD-1/PD-L1 blockade is a valuable addition to the therapeutic armamentarium against advanced NSCLC. However, multiple questions remain unanswered with the most prominent one being the pressing need to identify clinically relevant and reproducible predictive biomarkers. PD-1 blockade seems to be highly potent in a small subset of NSCLC patients; the high cost, the potential for serious adverse events, combined with the lack of benefit in approximately 75% of patients have led to efforts to identify patient subsets that derive significant benefit from immune checkpoint inhibition. One such putative biomarker that has been extensively evaluated in clinical trials is the level of PD-L1 expression. However, the use of archival rather than a recent tumour sample obtained on disease progression, the use of different IHC antibodies, the different positivity cut-offs across the various trials, the high rates of discordance between the primary and metastatic sites of disease, the possible contribution of PD-L2 in immune evasion in some tumours and the recognition that PD-L1 positivity at the tumour microenvironment is a dynamic event, currently render the inclusion of PD-L1 expression at the decision-making algorithm rather controversial [39]. Experience from clinical trials up to now, although immature, demonstrates that the overall survival for some of the immunotherapy agents seems very clearly associated with PD-L1 status, however, importantly, PD-L1 negativity cannot exclude durable responses to these drugs [17, 18]. Thus, in the KEYNOTE-001 trial of pembrolizumab, a cohort of patients with substantially better outcomes was distinguished using the cut-off of 50% for PD-L1 positivity. Still, lower or absent PD-L1 expression did not exclude sustained benefit [27, 29]. It is also important to note that the FDA approval for pembrolizumab only concerns PD-L1 positive tumours as determined by the PD-L1 IHC 22C3 pharmDx companion diagnostic, which was simultaneously approved with the drug. In contrast, although nivolumab was approved for use independently of PD-L1 status,

a different, optional complementary diagnostic test, the PD-L1 IHC 28-8 pharmDx was also approved to help clinicians determine which patients may benefit more. It is clear that a better understanding of the assay and its predictive performance, possibly in adjunct with additional IHC markers is needed before the universal use of PD-L1 for patient selection.

Other efforts in identifying predictive biomarkers focus on the population of infiltrating immune cells or on the mutational burden of the tumour, with the latter being supported by the high rates of response to pembrolizumab observed in tumours with mismatch repair deficiency and high mutation load [40]. A history of heavy smoking has also been shown to be a surrogate for higher mutation load and improved outcomes after treatment with nivolumab [18]. These and other novel biomarkers need to be prospectively evaluated and more data should be collected before their widespread application.

Other important considerations of PD-1/PD-L1 inhibitors in NSCLC are the optimal duration of treatment and combinations with other agents. In published clinical trials, nivolumab was either administered for 2 years or until disease progression. Contrary to conventional chemotherapy, treatment continuation with immune checkpoint inhibition even in the context of disease progression may confer additional benefit to patients. Thus, 9/23 patients from the CheckMate 017 and 16/71 from the CheckMate 057 trial that continued nivolumab despite initial disease progression (by RECIST 1.1), derived additional benefit, for a RR of 24% in this patient subset. However, no predictive factors for this type of response have been recognised and pseudoprogression is generally rare in NSCLC patients treated with anti-PD-1 directed therapy (only 3–5%); therefore, patients with clear clinical progression should be switched to alternative therapy.

It should be noted that the bulk of evidence for the use of immune checkpoint inhibitors in advanced NSCLC concerns patients with overt metastatic disease. The survival of patients with stage III NSCLC that receive definitive chemoradiotherapy remains poor mainly due to systematic disease progression [41]; efforts to improve outcomes by administering induction [42] or consolidation chemotherapy [43, 44] have failed. Moreover, the well-recognised abscopal effect [45], where antigens released by tumour irradiation may potentiate the immune response, provides the biologic rationale for the use of PD-1/PD-L1 blockade as consolidation therapy in this setting, a strategy that is being explored in the phase III PACIFIC trial. Finally, nivolumab evaluated as adjuvant treatment in high-risk resected melanoma was well tolerated and demonstrated immunologic activity with promising survival [46]. Since responses to immunotherapy tend to correlate with low disease burden [47], the use of immune checkpoint inhibitors to eradicate minimal residual disease seems as a logical next step.

Finally, new strategies are emerging in the field of immunotherapy of lung cancer including agents that augment co-stimulatory signals. Ongoing studies are focusing on 4-1BB (CD-137), OX40 (CD134), and CD-27 agonists that augment T-cell response, often in combination with checkpoint inhibitors. These receptors are members of the tumour necrosis factor receptor family and are primarily expressed on T-cells. When activated these receptors lead to T-cell proliferation and survival, as well as cytokine production. Therapeutic antibodies against these receptors are currently in clinical development [48].

6. The emerging role of PD-1 blockade in small cell lung cancer

SCLC has a distinct biology, natural history and treatment approach compared to NSCLC. Most patients present with widely disseminated disease and, despite its marked chemosensitivity and the initial impressive response rates to first-line platinum-based chemotherapy, resistance, disease progression and death commonly occur in a few months [49, 50]. Topotecan is the standard salvage treatment [51, 52]; however, median overall survival is poor at approximately 25 weeks and the drug is not well tolerated due to its propensity for serious myelotoxicity in previously treated patients.

Both nivolumab and pembrolizumab have demonstrated significant activity in early clinical trials in the treatment of relapsed or refractory SCLC. Data for two trials were presented at the 2015 American Society of Clinical Oncology meeting. In a phase I/II study, 128 patients with extensive SCLC unselected for PD-L1 expression and disease progression after platinum-based chemotherapy were treated with either nivolumab or the combination of nivolumab and ipilimumab. In the monotherapy arm, the ORR was 18% and in the combination arm 17%, with an additional 15% achieving partial responses after initial disease stabilization [53]. On the other hand, at the phase IB KEYONTE-028 trial, 24 patients with previously treated extensive stage SCLC selected for PD-L1 positivity (defined as membranous staining over 1% in tumour cells or inflammatory cells or positive staining in stroma) received pembrolizumab 10 mg/kg every 2 weeks. The ORR was 29.2% and the disease control rate was 33.3%; there were no complete responders. Responses were durable (median duration

of response 29.1 weeks) and treatment was well tolerated with the most common adverse events being asthenia, arthralgia, nausea and fatigue. The benefit was not correlated with PD-L1 expression levels, although this may due to the small size of the trial [54].

These preliminary results underscore the promise that immune checkpoint inhibition holds in the treatment of SCLC, a disease with virtually no treatment advances in systemic therapy during the previous decades. Larger confirmatory trials of PD-1 inhibition as consolidation therapy after first line platinum based chemotherapy are ongoing and will provide additional data regarding the role of immunotherapy in SCLC (NCT02359019, NCT02538666) and in other clinical settings as well, such as in relapsed / refractory disease (NCT02481830).

7. Conclusions

Following 50 years of disappointments, stagnation and lack of progress, in recent years the elucidation of the biology of NSCLC and of tumour–host interactions has led to tremendous leaps in the treatment of this devastating disease [55]. The driving force behind this progress is the rapid uptake of immunotherapy. Once a seldom used modality, it is now considered to be a standard antineoplastic treatment, along with surgery, radiation and chemotherapy. Having already established their superiority versus second line chemotherapy in advanced NSCLC, results of ongoing trials of PD-1 and PD-L1 inhibitors are eagerly awaited and will help answer many remaining questions. Furthermore, the recognition of multiple checkpoint inhibitors and agonists beyond PD-1 and CTLA-4 and the development of the respective drugs are expected to lead the way for changes in current oncology practice and may result in the transformation of advanced of NSCLC from a uniformly fatal to a chronic disease.

Author Contributions

AM: Initial concept, drafting of the manuscript
SA: Initial concept, drafting of the manuscript, critical revisions

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