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Targeting Programmed Cell Death -1 (PD-1) and Ligand (PD-L1): A new era in cancer active immunotherapy

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ABSTRACT

Improved understanding of the immune system and its role in cancer development and progression has led to impressive advances in the field of cancer immunotherapy over the last decade. Whilst the field is rapidly evolving and the list of drugs receiving regulatory approval for the treatment of various cancers is fast growing, the group of PD1- PDL-1 inhibitors is establishing a leading role amongst immunomodulatory agents.

PD1- PDL-1 inhibitors act against pathways involved in adaptive immune suppression resulting in immune checkpoint blockade. Within the last four years two PD-1 and three PD-L1 inhibitors have been utilized in clinical practice against a variety of malignancies. Focus was initially placed on targeting cancers considered immunogenic such as melanoma, renal and lung cancers but subsequently the application expanded to include amongst others Hodgkin Lymphoma, urothelial as well as head and neck cancer.

This article provides a comprehensive review of the early and late phase trials that led to the regulatory approval of all five PD1- PDL-1 inhibitors in the corresponding cancer types. It presents available data on the combinations of PD1- PDL-1 inhibitors with other therapies (immunotherapy, targeted therapy and chemotherapy), the toxicity profile of the PD1- PDL-1 inhibitors and ongoing trials testing the efficacy of these agents in cancer types beyond those that have been addressed already. Finally, current and future challenges in the application of PD-1 and PD-L1 inhibitors are discussed with emphasis on the role of predictive biomarkers.

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1. Introduction

Over the years, an improved understanding of the molecular mechanisms underlying immune regulation has led to the redirection of anticancer therapeutics towards immunotherapy. Despite initial controversy, some new well designed studies have come to underscore the discoveries about ligand-receptor interactions between cancer cells and host immune cells within the tumor microenvironment (TME). Some of these discoveries have already translated to clinical success in cancer therapeutics.

Abbreviations: TME, tumor microenvironment; FDA, Food and Drug Administration; DC, dendritic cells; CTLA-4, Cytotoxic T lymphocyte-associated molecule-4; PD-1, Programmed Death -1; PD-L1, Programmed Death Ligand; dMMR/MSI-H, DNA mismatch repair deficiency or a microsatellite instability-high; FFPE, formalin-fixed paraffin-embedded tissue.

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In this review, we provide background knowledge on the structure and function of the immune system, in particular the PD-1/PD-L1 pathway. Then, we present an overview of the clinical trials that supported the approval of the five PD-1/PD-L1 inhibitors currently available in clinical practice in cancer: nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and their combinations with other agents. Finally, we discuss current and future challenges in the application of PD-1 and PD-L1 inhibitors with emphasis on the role of predictive biomarkers.

1.1. Structure and function of the immune system

The immune system comprises two different components (e.g. innate and adaptive) which have overlapping actions. The innate component comprises dendritic cells, natural killer cells (NK), neutrophils, eosinophils, basophils, macrophages and mast cells. It functions as an organized network against foreign antigens without prior stimulation by antigens. In contrast, the adaptive immune component depends on antigen-presenting cells (APCs) in order to be activated and comprises of B lymphocytes (e.g. humoral immunity) and T lymphocytes (e.g. cellular immunity) including the CD4+ helper T lymphocytes and the CD8 + cytotoxic T lymphocytes (CTLs) (Fig. 1). The adaptive component avoids reacting with self-antigens by rendering immune cells inert (i.e. tolerance) (Daley, The, Hu, Strasser, & Gray, 2017). This occurs via the two-signal model of activation in which two signals from antigen presenting cells (APCs) are required. The first is antigen dependent and consists of the interaction of the antigenic peptide and the major histocompatibility complex (MHC) with the T-cell receptor (TCR) while the second co-stimulatory signal is transmitted by molecules expressed on APCs targeted to specific receptors on the T-cells. When a T-cell receives only the first signal it becomes anergic to subsequent antigenic stimulation (Appleman & Boussiotis, 1999). Furthermore, there are receptors that deliver negative co-inhibitory signals and act as "immune checkpoints" which are important in maintaining tolerance and protecting against autoimmunity (Nishimura, Nose, Hiai, Minato, & Honjo, 1999).

The B7-1/B7-2 - CD28/CTLA4 pathway is the best studied of the T-cell costimulatory pathways and plays an important role in the T-cell activation or tolerance. In this pathway, a fine balance occurs between CD28 "co-stimulation" mediated activation of T-cells and CTLA4 immune-checkpoint mediated inhibition of T cells (Salomon & Bluestone, 2001). Programmed cell death 1 (PD-1) comes as an inhibitory receptor along with its ligands and enhances the importance of immune checkpoint to maintain self-tolerance (Barber et al., 2006). Malignant cells are able to evade immune destruction by modulation of the immune checkpoint pathways but also by increasing the co-inhibitory ligand expression (such as PD-L1) thereby rendering tumor-infiltrating lymphocytes ineffective against the tumor despite being present in the TME (Ahmadzadeh et al., 2009).

1.2. The PD-1/PD-L1 pathway

PD-1 was first discovered in 1992 as a 288 amino acid protein expressed on the surface of T-cells and associated with apoptosis (Ishida, Agata, Shibahara, & Honjo, 1992). Subsequent reports showed that PD-1 deficient mice exhibit autoimmunity (lupus-like arthritis, glomerulonephritis and splenomegaly with predominantly IgG3 deposition) in addition of PD-1 being a negative regulator of immune response (Nishimura et al., 1999). Furthermore, PD-1 deletion in Balb/c mice results in dilated cardiomyopathy, gastritis and high serum

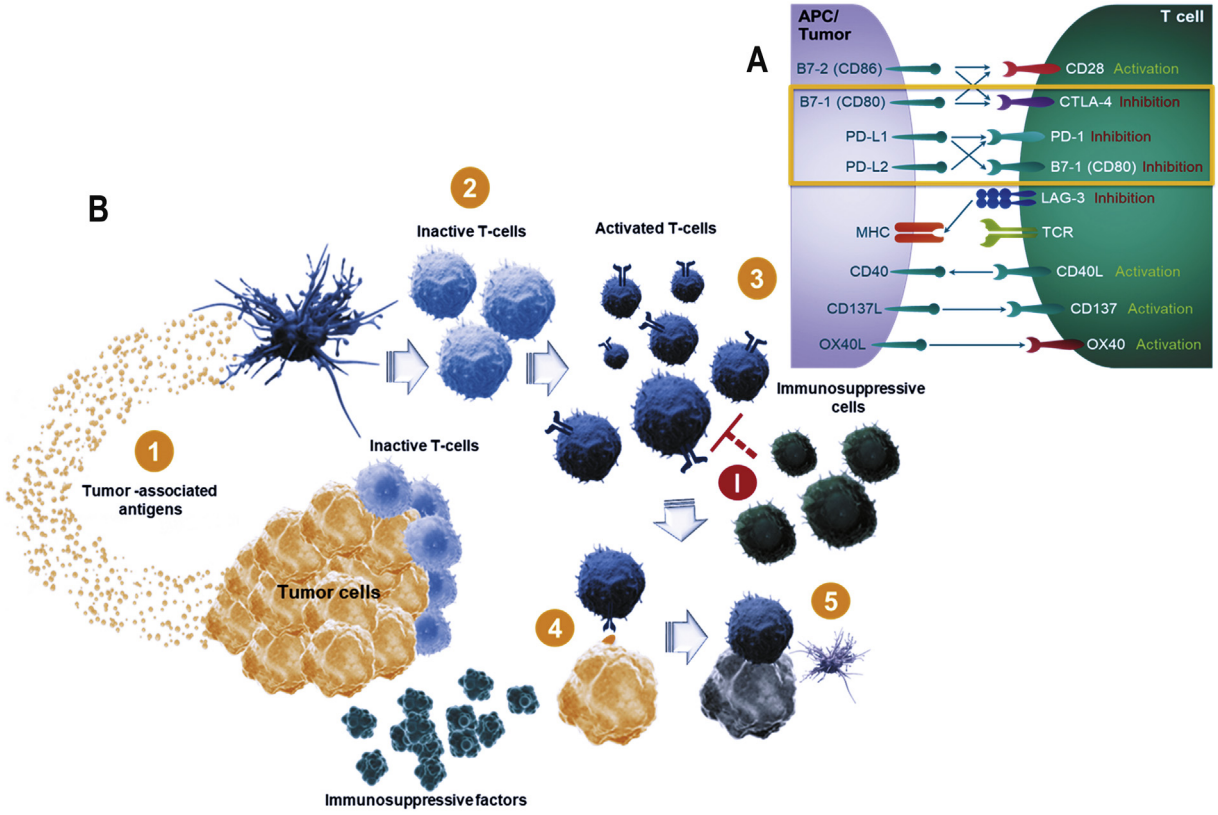

Fig. 1. A. Inhibitory or activation effects of interactions between the surface membrane receptors on antigen presenting cells (APC) or tumor cells and T-lymphocytes; B. T-Cell antitumor response. 1: Tumor antigens released by tumor cells, 2: Tumor antigens presented to T cells, 3: T cells are activated - they proliferate and differentiate into effector and memory cells, 4: Effector T cells recognize tumor antigens, 5: T cells kill tumor cells. Tumors use complex, overlapping mechanisms to evade and suppress the immune system, producing ineffective presentation of tumor antigens (e.g. downregulation of MHC I), with the recruitment of immunosuppressive cells with inactive T cells (e.g., Tregs, MDSCs) (I), with T-cell checkpoint dysregulation (e.g., PD-1, CTLA-4), releasing of immunosuppressive factors (e.g., TGF-β, IDO, IL-10).

troponin reactive IgG1 (Nishimura et al., 2001) whereas in MRL mice lethal myocarditis is accelerated with the introduction of the lpr mutation (Nishimura et al., 1996; Wang et al., 2010). Homozygous PD-1 null 2C-TCR (anti-H-2Ld) transgenic mice in the H-2b/d background develop a chronic graft-versus-host-like disease (Nishimura et al., 1999). Taken together, this information confirms that PD-1 is a molecule that limits T-cell activation and proliferation while it promotes self-tolerance. This, in turn, suggests that PD-1 mainly regulates late-phase immune responses in the periphery such as in chronic infection, effector phase and memory response.

The ligand for PD-1 was initially identified as B7-H1, a molecule homologous to B7-1/B7-2 that did not interact with ICOS, CD28 or CTLA4 (Dong, Zhu, Tamada, & Chen, 1999). It was later found to be the ligand for PD-1, hence named PD-L1 (*Pdcd1lg1*, CD274) (Freeman et al., 2000). The second ligand to PD-1, PD-L2 (Pdcd1lg2, CD273) was discovered a year later (Latchman et al., 2001).

1.2.1. Molecular structures of the components of the PD-1/PD-L1 pathway

PD-1 is an amino-acid chain with an extracellular region consisting of i) a single N-terminal IgV-like domain (sharing homology with CD28, CTLA4, ICOS thus a member of the B7-1/B7-2 - CD28/CTLA4 superfamily), ii) a 20-amino-acid stalk separating the extracellular region from the plasma membrane, iii) a transmembrane domain and iv) a cytoplasmic region that contains two tyrosine-based signal motifs. In contrast to other members of the superfamily (that have an unpaired cysteine to allow them to homodimerize on the cell surface) PD-1 most likely exists as a monomer on the cell surface (Zhang et al., 2004). Furthermore, it does not have any –SH2 or –SH3 groups thus it uses two other intracellular motifs: i) a tyrosine-based signal one that is an immunoreceptor inhibitory motif (ITIM) formed by N-terminal sequence VDYGEL required for recruiting –SH2 domain containing phosphatases (Neel, Gu, & Pao, 2003) and ii) an immunoreceptor witch-motif (ITSM) formed by a C-terminal TEYATI sequence that carries out the inhibitory function of PD-1 (Chemnitz, Parry, Nichols, June, & Riley, 2004) (Fig. 2).

PD-L1 and PD-L2 ligands are type I glycoproteins (consisting of IgV and IgC domains) sharing a 34% homology whereas their homology with the other superfamily B7 members is 20%. Mic3 and human PD-1 share about 60% identity. PD-1 utilizes its front β-sheet (AGFCC′ β-strands) to bind to the front β-sheet of PD-L1 (AGFCC′ β-sheet) or PD-L2 IgV domains (AGFC) (Lazar-Molnar et al., 2008).

PD-1 is expressed on dendritic cells (DCs), B cells, activated T cells (both CD4+, CD8+), natural killer cells (NK). It is expressed on activated T cells at the late effector phase especially during chronic viral infections on exhausted CD8+ cells (Barber et al., 2006). PD-L1 is expressed on different cell types, including T-cells, epithelial cells, endothelial cells and it is upregulated in many tumors - as a mechanism of immune evasion - either in cancer cells or in the TME (including antigen-presenting cells) (Dong et al., 2002). PD-L2 is mainly expressed on dendritic cells and monocytes, but can be induced in other cells as well (Yearley et al., 2017). A substantial proportion of solid tumors and hematological malignancies have been demonstrated to have increased expression of the two targetable immune checkpoint proteins PD-1 and PD-L1 (Annibalia et al., 2018Gatalica et al., 2014).

2. From bench to bedside: targeting the PD-1/PD-L1 pathway in cancer patients

Immunotherapy consists of a variety of approaches encompassing immune-modifying agents (cytokines and vaccines), oncolytic viruses, adoptive cell therapy, as well as immune checkpoint inhibitors. The term passive therapy refers to the administration of cytokines, antibodies and immune cells to patients to initiate an antitumor action without however generating an immunological memory (Rescigno, Avogadri, & Curigliano, 2007). In contrast, active immunotherapy, stimulates the patient's immune system to produce an antigen-specific antitumor

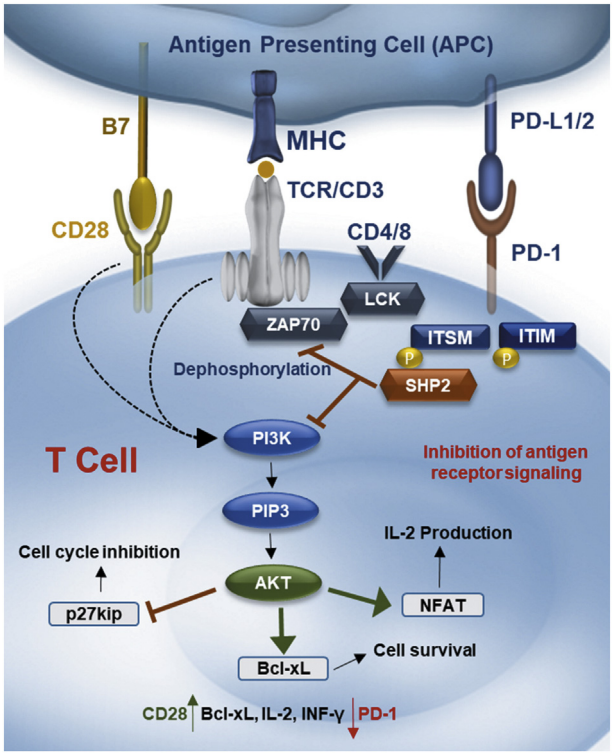

Fig. 2. PD-1 signaling pathway inhibits TCR signaling. PD-1/PD-L1,2 complex formation induces phosphorylation of the intracellular immunoreceptors tyrosine-based switch motif (ITSM) and tyrosine-based inhibitory motif (ITIM) in PD-1 cytoplasmic tail. SHP-2 binds to phosphorylated ITSM and leads to inhibition of T cell receptor (TCR) through Zap-70 dephosphorylation, producing PI3K/Akt pathway abolition. This generates many downstream effects, such as downregulation of the Bcl-xL and NFAT pathways affecting cell survival and cell proliferation, p27kipl accumulation, IL-2, INF-gamma production.

effect (McNeel, 2007) resulting in a durable response. Immune checkpoint blockade refers to the suppression of inhibitory pathways activated by cancer cells and comprises antibodies directed against pathways involved in adaptive immune suppression such as CTLA-4, and PD-1 and PD-L1.

The first checkpoint inhibitor to be approved by the US Food and Drug Administration (FDA) in 2011 was ipilimumab, a CTLA-4 inhibitor, for the treatment of patients with metastatic melanoma, following demonstration of survival benefit in a phase III clinical trial (Hodi et al., 2010). This has opened up new possibilities in the management of cancer and within a few years led to the introduction of other CTLA-4 inhibitors as well as several PD-1 and PD-L1 inhibitors thus establishing a role for immune checkpoint blockade approaches in oncology (Fig. 3). Finally, the PD-1/PD-L1 inhibitors appear to have a better toxicity profile in terms of severity of side effects and manageability when compared to CTLA-4 inhibitors (Brahmer et al., 2012).

2.1. Approved applications of PD-1/PD-L1 pathway inhibitors

There are currently five FDA-approved PD-1/PD-L1 immune checkpoint inhibitors in cancer therapeutics: nivolumab, pembrolizumab, atezolizumab, durvalumab and avelumab. The introduction of these agents in clinical practice – primarily the first two, nivolumab and pembrolizumab - has transformed the management and improved the outcomes of certain cancer types within a few years. PD-1 and PD-L1 checkpoint inhibitors being either under investigation or approved for use in cancer are shown in Table 1.

2.1.1. Nivolumab (anti-PD-1 monoclonal antibody)

Nivolumab (Opdivo, Bristol-Myers Squibb), is a humanized monoclonal IgG4 anti-PD-1 antibody approved for the treatment of

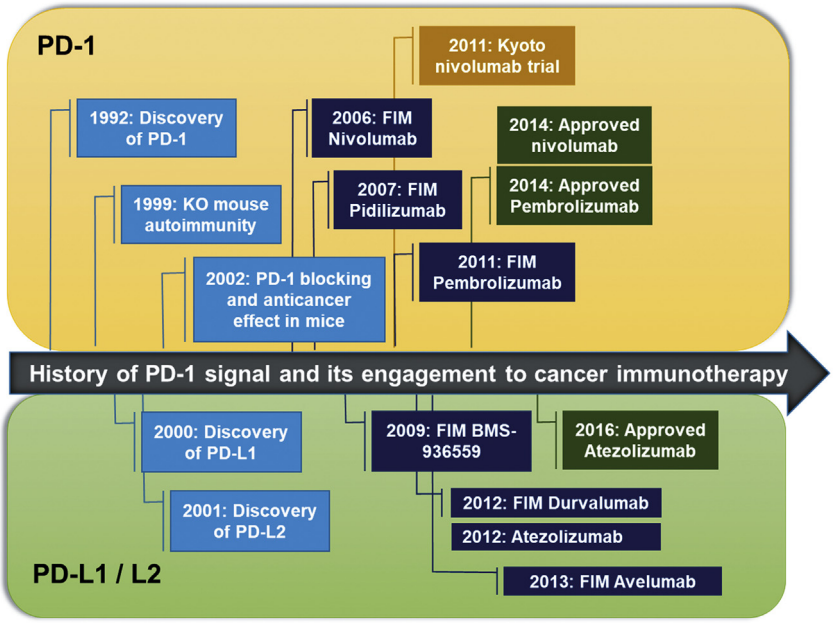

Fig. 3. Timeline of PD-1 discovery and PD-L1/2 antibodies development. FIM: First in man; Approved: FDA approved.

unresectable, metastatic or completely resected (adjuvant) melanoma, metastatic NSCLC, urothelial cancer, advanced renal cell carcinoma (RCC), head and neck cancer (HNSCC), Hodgkin Lymphoma, colorectal carcinoma and hepatocellular carcinoma. Its mechanism of action comprises binding to the PD-1 receptor and blocking of its interaction with both PD-L1 and PD-L2, thus releasing a PD-1 pathway mediated immune response against tumor cells (Brahmer et al., 2010; Tykodi et al., 2012).

Melanoma: The first approval for the use of nivolumab in advanced disease came in 2014 for unresectable or metastatic melanoma based on

Table 1
PD-1 and PD-L1 inhibitors under investigation or approved for use in cancer[a].

Target	Molecule	Ab type	Approved in	Company	Commercial name
PD-1	Nivolumab (BMS-936558, MDX1106, ONO4538)	Human IgG4	Melanoma, NSCLC, RCC, Hodgkin's, HNSCC, Urothelial cancer	Bristol-Meyers Squibb/Ono	Opdivo
	Pidilizumab (MDV9300, CT-011)	Humanized IgG1k		Cure Tech	
	Pembrolizumab (MK-3475, Lambrolizumab)	Humanized IgG4	Melanoma, NSCLC, HNSCC, Hodgkin's, MMR or MSI high cancers	Merck	Keytruda
	Spartalizumab (PDR001)	Humanized IgG4		Novartis	
	AMP-514 (MEDI-0680)	PD-L2 fusion molecule		Amplimmune/MedImmune/Astrazeneca	
	AMP-224	PD-L2 IgG2a fusion molecule		Amplimmune/GlaxoSmith Klein	
	JS001	Humanized IgG4		Shangai Junshi Biosciences	
	Tislelizumab (BGB-A317)	Humanized IgG4		Beigene/Celgene	
	GLS-010 (WBP3055)	Human IgG4		Gloria/Wuxi/Arcus	
	IBI-308	Human IgG4		Innovent/Lilly	
	Cemiplimab (REGN-2810, SAR-439684)	Human IgG4		Regeneron/Sanofi	
	Genolimzumab (GB-226)	Humanized IgG4		Genor/CBT	
	Camrelizumab (INCSHR-1210; SHR-1210)	Humanized IgG4		Jiangsu/Incyte	
	CA-170 (AUPM-170)[a]			Aurigene/Curis	
	PF-06801591			Pfizer	
	TSR-042	Human IgG4		AnaptysBio/Tesaro	
PD-L1	Atezolizumab (MPDL3280A)	Humanized IgG1k	NSCLC, Urothelial cancer	Roche/Genentech	Tecentriq
	Durvalumab (MEDI4736)	Human IgG1k		MedImmune/AstraZeneca/Celgene	Imfinzi
	Avelumab (MSB0010718C)	Human IgG1	Gastric cancer (EMA), Merkel cell carcinoma (FDA)	Merck Serono/Pfizer	Bavencio
	BMS-936559 (MDX1105)	Human IgG4		Bristol-Meyers Squibb	
	CA-170 (AUPM-170)			Aurigene/Curis	
	M-7824 (MSB-0011359-C)	Fusion molecule PD-L1/CD274 bound to TGF-βRII		Merck Serono	
	LY-3300054			Lilly	
	SHR-1316	Humanized IgG4		Jiangsu Hengrui	
	JNJ-61610588	Human IgG1k		Janssen	
	KN035	Monoclnal		Alphamab/3D Medicines	

[a] PD-1, PD-L1, VISTA inhibitor, HNSCC, head and neck squamous cell carcinoma;MMR, mismatch repair;MSI, microsatellite instability; NSCLC, non small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer

the results of an open-label phase III clinical trial (CheckMate-037) randomizing patients to nivolumab or to investigator's choice of chemotherapy (dacarbazine or carboplatin), following previous treatment with ipilimumab or a BRAF inhibitor. The overall response rate was significantly higher with nivolimab – 31.7% (95% CI 23.5-40.8) - compared to 10.6% (95% CI 3.5 -23.1) in patients treated with chemotherapy (Weber et al., 2015). In another phase III trial, CheckMate-066, nivolumab improved OS by 58% and PFS by 57% compared with dacarbazine (Robert et al., 2015a). In fact, at the interim analysis, in view of the impressive results, the study was unblinded and patients treated with chemotherapy were allowed to switch to nivolumab. In PD-L1-positive patients, in particular, OS was improved by 70% and ORR was 52.7% versus 10.8%, for nivolumab and dacarbazine, respectively.

Impressively, in just over 3 years from its initial approval as a single agent in the second line setting for melanoma (2014), in December 2017, nivolumab was granted FDA approval as adjuvant therapy for patients with completely resected melanoma with lymph node involvement or metastatic disease, based on the results of the phase III CheckMate-238 trial (Weber et al., 2017). In this study, in surgically resected patients with stages IIIB, IIIC, and IV melanoma (considered to have a 50% or greater risk of relapse over 5 years), nivolumab led to a 13% absolute increase in relapse-free survival versus the active comparator ipilimumab (Weber et al., 2017).

Lung cancer: The initial approval of Nivolumab by the FDA was based on the results of two large randomized phase III studies which reported statistically significant survival benefit for nivolumab versus docetaxel in platinum – refractory advanced NSCLC. The CheckMate 017 trial included patients with squamous NSCLC (Brahmer et al., 2015) whereas the CheckMate 057 one included patients with non-squamous NSCLC (Borghaei et al., 2015). However, in the phase III CheckMate 026 trial, when compared to standard chemotherapy in the first line setting in previously untreated stage IV or recurrent NSCLC, with a PD-L1 expression level of 5% or more, nivolumab was not associated with significantly longer progression-free survival than chemotherapy (Carbone et al., 2017). A number of reasons accountable for this result could relate to patient selection which is recognized as one of the main hurdles in conducting immunotherapy trials. This and other challenges in the application of PD-1 and PD-L1 inhibitors in clinical practice are discussed separately in this review. Finally, the role of nivolumab in the adjuvant setting in NSCLC is currently being evaluated in prospective randomized controlled clinical trials [ClinicalTrials.gov Identifier: (NCT02595944)].

Urothelial carcinoma: The results of the phase II CheckMate 275 trial (which enrolled patients with advanced or metastatic urothelial cancer to receive nivolumab following failure of platinum based first line chemotherapy) led to FDA approval in February 2017 (Sharma et al., 2017). Overall response rate was higher in patients with high PD-L1 expression (28.4% for PD-L1 ≥5%, 23.8% for PD-L1 ≥1%, and 16.1% for PD-L1 < 1%) whereas OS rate was also higher for tumors with PD-L1 expression of ≥1% versus PD-L1 < 1%.

Renal cancer: Nivolumab has been available for use in advanced renal carcinoma since 2015 based on the efficacy and safety results of an opel-label randomized phase III study (CheckMate 025) which demonstrated survival benefit in favor of nivolumab when compared to everolimus in patients who had received one or two prior antiangiogenic therapies (Motzer et al., 2015). Survival benefit was observed in every subgroup receiving nivolumab, over everolimus irrespective of PD-L1 expression.

HNSCC: In the CheckMate 141 (a randomized phase III) study, patients with progressive or recurrent disease (following first line platinum based therapy) received nivolumab or investigator's choice chemotherapy (Ferris et al., 2016). Nivolumab was associated with significantly longer OS compared to standard therapy [7.5 months (95% CI, 5.5 - 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 - 6.0) in the standard therapy arm] while the estimates of the 1-year survival rate were approximately 19% higher with nivolumab than with standard therapy (36.0% vs. 16.6%). FDA approval was granted in 2016.

Hodgkin Lymphoma: In 2016, through an expedited review process and based on two single-arm, phase II, multicenter trials in adults with classical Hodgkin Lymphoma (HL) (CheckMate-205 and CheckMate-039), FDA included nivolumab to the therapeutic portfolio for advanced HL in relapsed or refractory disease (Ansell et al., 2015; Younes et al., 2016). This was the first FDA application and approval for a PD-1 inhibitor as treatment for hematological malignancies and it was based on the improved response rate and duration demonstrated in these two single-arm phase II studies.

Colorectal cancer: Based on the results of the CheckMate 142 trial, nivolumab was approved in DNA mismatch repair deficiency or a microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer refractory to fluoropyrimidine, oxaliplatin, and irinotecan in 2017 (Overman et al., 2017). In this phase II trial, patients received nivolumab as a single agent and 31% of them was shown to achieve overall response by RECIST 1.1 irrespective of the PD-L1 levels.

Hepatocellular carcinoma: One of the latest approvals for Nivolumab, at the end of 2017, was for advanced hepatocellular carcinoma following failure of sorafenib during the phase I/II escalation and expansion CheckMate 040 trial (El-Khoueiry et al., 2017). Overall response rate reached an impressive 20% (95% CI 15-26%) in patients treated with nivolumab (at 3mg/kg) in the dose-expansion phase and 15% (95% CI 6-28%) in the dose-escalation phase with 25% of patients experiencing grade 3 or above toxicity which was nevertheless manageable.

2.1.2. Pembrolizumab (anti-PD-1 monoclonal antibody)

Pembrolizumab (Keytruda, Merck & Co/MSD) is a humanized mAb targeting PD-1. It is approved for use against unresectable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC), advanced urothelial cancer, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), advanced gastric cancer, classic HL, and against any unresectable or metastatic solid tumor with dMMR/MSI-H state or colon cancer that exhibits progression under treatment. Its mechanism of action is similar to that of Nivolumab in that it disrupts the binding of PD-1 with its immune-suppressing ligands (PD-L1 and PD-L2) inhibiting restoration of T-cell response and consequently an immune response.

Melanoma: The role of pembrolizumab in advanced melanoma was explored in the Phase I KEYNOTE 001 trial (and expansion cohorts) and subsequently in the phase II and III KEYNOTE 002 (Ribas et al., 2015) and 006 (Robert et al., 2015b; Schachter et al., 2017) trials respectively. These studies were conducted to show that pembrolizumab significantly improves overall response and survival rates (OS and PFS) compared to ipilimumab (in ipilimumab-naïve patients; KEYNOTE 006), and significantly improves overall response rates and PFS, but not OS, compared to chemotherapy in ipilimumab-refractory patients (who had also received BRAF/MEK inhibitor therapy if BRAF-mutation positive; KEYNOTE 002). In all settings, Pembrolizumab was well tolerated at the doses tested (e.g. 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks). Approval of Pembrolizumab for use in the second line setting in unresectable or metastatic melanoma was based on the KEYNOTE 001 trial whereas subsequent approval for use in the first line setting on the KEYNOTE 002 and 006 studies was immediately followed.

Lung cancer: Pembrolizumab can be used in the management of NSCLC in first and second line settings. In the KEYNOTE-010 trial (a randomized phase II/III trial) patients with previously treated NSCLC and at least 1% PD-L1 expression, received either pembrolizumab (at 2 mg/kg or 10 mg/kg) or docetaxel (the standard of care therapy in the second line setting) in patients with EGFR mutation or ALK rearrangement following failure of platinum- based chemotherapy or a tyrosine kinase inhibitor (Herbst et al., 2016). Pembrolizumab was shown to prolong overall survival particularly in those with strong PD-L1 expression (at least 50%expression) and so FDA approval was therefore restricted to

those tumors expressing PD-L1 only. Subsequently the KEYNOTE 024 trial, randomized patients with advanced and PD-L1-positive NSCLC to receive pembrolizumab (in the first line setting versus standard of care platinum-based chemotherapy) and demonstrated statistically significant prolongation of survival [from 6.0 to 10.3 months (HR) 0.50; 95% CI, 0.37–0.68; P <0.01]. Importantly, toxicity was tolerable and quality of life was improved compared to platinum based chemotherapy. These results led to the approval of Pembrolizumab as first line monotherapy in metastatic NSCLC, by FDA, in cases where tumor expression of PD-L1(TPS) is ≥50% and no EGFR- or ALK-positive tumor alterations are detected (Reck et al., 2016).

Urothelial cancer: The use of pembrolizumab in the second line setting in urothelial cancer has been based on the results of the Keynote-045 randomized phase III open-label trial which assigned patients with recurrent or progressive disease (following platinum-based therapy) to either investigator's choice of chemotherapy or pembrolizumab (Bellmunt et al., 2017). Overall response rate and median OS in the pembrolizumab arm were statistically significantly higher when compared to the chemotherapy arm (21.1% vs. 11.4%, P = 0.001) and (10.3 months CI 8.0-11.8 vs. 7.4 months CI 6.1-8.3, P = 0.002) respectively. Pembrolizumab has also been approved for use in the first-line therapy in cisplatin ineligible patients based on preliminary results from the single arm phase II Keynote-052 trial. This study showed overall response rate of 27% (95% CI 22-32) for all 370 patients with 6 month PFS and OS rates of 31% and 67% respectively (Balar et al., 2016). Toxicity in both studies was withib acceptable limts thus leading to FDA approval for both indications.

HNSCC: The KEYNOTE 012 phase Ib clinical trial examined safety and efficacy of single agent pembrolizumab in the management of pretreated patients with advanced head and neck cancer and a PD-L1 expression of >=1%. Safety of the drug was deemed acceptable and overall response rate was 18% (95% CI 8-32%) (Seiwert et al., 2016). These results led to accelerated approval by FDA for the use of pembrolizumab in head and neck cancer.

Gastric cancer: In September 2017, pembrolizumab was granted its latest approval for previously treated patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) cancer whose tumors express PD-L1. This was based on the results of the multicenter, non-randomized, open-label, KEYNOTE-059 trial which enrolled patients with gastric or GEJ adenocarcinoma who progressed on at least two prior systemic treatments for advanced disease. The objective response rate of 13.3% (95% CI, 8.2-20.0), the duration of response ranging between 2.8+ months and 19.4+ months, the median PFS of 2 months and the median OS of 5.6 months (with a 12-month OS rate of 23.4% months) were considered encouraging and sufficient to provide approval of pembrolizumab in this setting whilst the results of a confirmatory trial are awaited (Fuchs et al., 2017).

Hodgkin Lymphoma: In the KEYNOTE-087 trial, patients with relapsed or refractory classical HL were treated with either i) single agent pembrolizumab [following autologous stem cell transplantation (ASCT) and subsequent brentuximab vedotin (BV)] or ii) salvage chemotherapy and BV (with chemoresistant disease) or iii) ASCT but without BV after transplantation. In all three groups, the overall response rate was high (73.9%, 64.2% and 70% respectively) and toxicity was manageable as well (Chen et al., 2017). These results led to the only approval of pembrolizumab for a hematological malignancy.

Microsatellite instability high (MSI-H) or mismatch repair deficient (d-MMR) cancers: In May 2017, FDA approved the use of pembrolizumab for patients with any treatment-refractory unresectable or metastatic primary tumors bearing either of these two types of mutations (both of which disrupt DNA repair). A number of trials have shown impressive response rates with pembrolizumab in patients with MSI-H and d-MMR beyond colorectal cancer (Diaz et al., 2016; Le et al., 2015). In fact, the response rates in non-colorectal (MSI-H) cancers appear to be particularly encouraging based on data from ongoing multicenter phase II studies including the KEYNOTE-158 (noncolorectal) and KEYNOTE-164 (colorectal) ones. The overall response rate is reported as 42.9% (95% CI, 21.8-66.0%) for non colorectal MSI-H and 26.2% (95% CI, 15.8-39.1%) for colorectal MSI-H cancers (Diaz et al., 2017).

2.1.3. Atezolizumab (anti-PD-L1 antibody)

Atezolizumab (Tecentriq, Genetech/Roche), is an IgG1 mAb against PD-L1, which has been approved to treat metastatic NSCLC and locally advanced or metastatic urothelial carcinoma in first and second line setting. Atezolizumab binds to the ligand PD-L1 on tumor cells resulting in a dual blockade of the PD-L1 binding to its inhibitory receptors PD-1 and B7.1

Urothelial cancer: Since 2016, the approved indication of atezolizumab is for patients with locally advanced or metastatic urothelial carcinoma who have either failed chemotherapy (second line setting) or who are platinum-ineligible in the first line setting. The results of the IMVigor multicenter phase II study (Rosenberg et al., 2016) showed an improved overall response rate of 15% (compared to the 10% control rates) and a correlation of response with PD-L1 expression (PD-L1 ≥ 5% showed a 27% response, PD-L1 ≥ 1% showed 18% response and PD < 1% showed 8% response). However, this was not the case with OS where patients with PD-L1 ≥ 5% had an OS of 12.3 months compared to those with PD-L1 < 5% and an OS of 19.1 months (Balar et al., 2017b).

NSCLC: Based on the results of the phase II POPLAR (Fehrenbacher et al., 2016) and phase III OAK (Rittmeyer et al., 2017) trials, atezolizumab was approved for patients with pretreated metastatic NSCLC. In both studies, patients were randomized to receive atezoluzimab versus standard second line chemotherapy (with docetaxel). In both trials, significant OS benefit was achieved, in favor of atezoluzimab while even more benefit was documented in patients with greater PD-L1 expression.

2.1.4. Avelumab (anti- PD-L1 antibody)

Avelumab (Bavencio, Merck KGaA and Pfizer) is a fully humanized monoclonal IgG1 antibody against PD-L1. Since May 2017, it is approved for the management of advanced or metastatic Merkel cell carcinoma while its use for urothelial cancer has been granted since December 2017.

Merkel cell carcinoma: Approval for this rare malignancy was based on the results of the JAVELIN phase II trial in which patients with advanced or metastatic disease (pretreated with one or more lines of chemotherapy) received avelumab until progression (Kaufman et al., 2016). The overall response rate was 31.8% (95% CI 21.9-43.1) whilst in tumors with PD-L1 expression of >=1%, over 1/3 achieved objective responses. Toxicity was reported to be mainly hematological.

Urothelial cancer: Accelerated FDA approval was granted to avelumab for the treatment of patients with platinum-refractory metastatic urothelial carcinoma based on the pooled analysis from two expansion cohorts of the open-label phase I trial dose-expansion JAVELIN Solid Tumor study (Patel et al., 2018). With a follow up of at least 6 months, an overall response rate of complete or partial response was recorded in 27 patients (17%; 95% CI 11–24), including 9 complete responses (6%) and 18 partial (11%) ones. The toxicity was also recorded as being manageable.

2.1.5. Durvalumab (anti- PD-L1 antibody)

Durvalumab (Imfinzi, Medimmune/AstraZeneca) is a human immunoglobulin G1 kappa monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80. It is approved for use in locally advanced NSCLC as well as advanced urothelial cancer.

NSCLC: In February 2018, based on the results of the phase III PACIFIC trial, durvalumab was approved for the treatment of patients with locally advanced, unresectable stage III NSCLC who did not progress following chemoradiotherapy (Antonia et al., 2017). In this trial,

durvalumab improved median PFS by 11.2 months compared to placebo (16.8 vs 5.6 months; HR, 0.52; 95% CI, 0.42-0.65; P < .0001). The 12-month PFS rate was 55.9% (versus 35.3%) and the 18-month PFS rate was 44.2% (versus 27.0%) in favor of the anti-PD-L1 agent. The results were irrespective of PD-L1 status.

Urothelial cancer: The 1108 phase I/II study included patients with platinum-refractory advanced or metastatic cancer at the second line setting (Massard et al., 2016). Recent results have shown that whilst overall response rate was 17.8% in all patients (95% CI 12.7-24.0), response rate amongst those with a PD-L1 expression of >=25% was 27.6% (95% CI 19.0-37.5) and much lower in patients with PD-L1 negative expression of 5.1% (95% CI 1.4-12.5) (Hahn et al., 2017). FDA approval was granted in May 2017.

2.2. Inhibition of PD-1/PD-L1 axis in other cancer types

A number of clinical trials are currently investigating the therapeutic potential of checkpoint inhibition in cancer types that are considered to be less immunogenic. Ongoing trials are exploring this strategy in breast, ovarian and central nervous system (CNS) tumors as well as in sarcoma. Whilst the results are not overwhelmingly positive, encouraging data are documented for certain subtypes of each of these malignancies. However, presentation of such data is beyond the scope of this article.

In breast cancer, higher PD-L1 expression and TILSs presence has been shown in triple negative breast cancer compared to hormone receptor positive one (Loi et al., 2014; Mittendorf et al., 2014). Results demonstrating long lasting efficacy and acceptable toxicity have been reported with pembrolizumab (Nanda et al., 2016; Nanda et al., 2017a) whilst early phase trials are examining the role of nivolumab in the advanced/metastatic setting either as monotherapy (NCT02499367) or as combination therapy (NCT02834247). Studies on atezolizumab, durvalumab and avelumab are also ongoing.

In ovarian cancer, it appears that in high-grade serous cancers PD-L1 expression is associated with tumor-infiltrating T cells and favorable prognosis (Webb, Milne, Kroeger, & Nelson, 2016). Early phase monotherapy clinical trials with nivolumab (Hamanishi et al., 2015) and pembrolizumab (Varga et al., 2017) have demonstrated some durable antitumor activity and an acceptable toxicity profile. Interesting concepts including a combination trial with olaparib or cediranib showed both activity and tolerability (Lee et al., 2017).

Blocking the PD-1/PD-L1 pathway appears to be a potential new treatment strategy in gliomas/glioblastomas despite that the CNS may be lacking immuno-surveillance. Ongoing trials have primarily included combinations with either chemotherapy or targeted agents and early results from the CheckMate 143 trial (comparing the effectiveness and safety of nivolumab versus bevacizumab in glioblastoma patients) have shown no OS benefit for nivolumb leading to the discontinuation of this arm (Reardon et al., 2017).

Finally, in sarcoma, nivolumab and pembrolizumab have been tested as monotherapy in the advanced setting (Burgess et al., 2017). Recent reports show that pembrolizumab is generally well tolerated for patients with advanced sarcomas while it also shows promising activity in certain subtypes (e.g. undifferentiated pleomorphic sarcoma, liposarcoma; Clinical trial information: NCT02301039).

2.3. Combination of PD1/PD-L1 inhibitors with other therapies

The aim of any combination strategy in cancer therapy is to improve efficacy by overcoming diversity of response and development of resistance whilst maintaining acceptable toxicity. In the field of immunotherapy, emphasis has been placed on combination strategies with the number of trials increasing dramatically over the last 5 years. Promising combinations of the PD1/PD-L1 inhibitors explored to date include those with: (i) other immune checkpoint inhibitors, (ii) targeted therapies and (iii) chemotherapy.

2.3.1. Combination of PD1/PD-L1 inhibitors with other immune checkpoint inhibitors

The concept of combining PD1/PD-L1 inhibitors with other checkpoint inhibitors - namely CTLA-4 inhibitors - has been under exploration for some time now. The rationale behind this combination is that CTLA-4 and PD1 checkpoints regulate different signaling pathways (the CTLA-4 checkpoint is critical for T cell priming and activation, whereas PD1 blocks effector T cell responses in tissues) despite both being expressed on T lymphocytes.

Not long after the establishment of each agent as a monotherapy, Wolchok et al. (2013) reported the results of a phase I trial combining ipilimumab and nivolumab in patients with advanced melanoma showing an objective response in 53% of them together with 80% (or more) of tumor reduction. In comparison, the sequenced regimen (patients previously treated with ipilimumab received nivolumab) shown an objective response rate of 20% (Wolchok et al., 2013). In addition, grade 3 or 4 adverse events were experienced by 53% in the combination regimen versus 18% in the sequenced-group. However, the side effects were similar to those observed in monotherapy and were generally reversible (Wolchok et al., 2013).

The clinical benefit of the combination trial (versus CTLA-4 inhibition alone) was consolidated by the results of a subsequent phase III study which compared ipilimumab alone to inivolumab alone and to their combination, in patients with advanced melanoma, demonstrating superiority in overall survival with combination therapy or with nivolumab alone compared to ipilimumab alone (Larkin et al., 2015; Wolchok et al., 2017).

Based on results from the randomized phase III CheckMate 069 trial, in 2015, FDA granted approval for a checkpoint inhibitor combination of nivolumab with ipilimumab as first-line treatment for BRAFV600-wildtype unresectable or metastatic melanoma, (Postow et al., 2015). The combination of nivolumab with ipilimumab resulted in an objective response of 61% of patients with BRAFV600-wild-type tumors compared with 11% in the monotherapy group with the overall response being independent of the PD-L1 status. Grade 3 and above adverse events were more common in the combination arm (52% vs 24% in the monotherapy arm) but they were manageable. Subsequently, nivolumab and ipilimumab combination received a further approval for unresectable or metastatic melanoma irrespective of BRAFV600 mutation status (based on results of the phase III CheckMate 067 trial). This study demonstrated an overall OS benefit for the combination therapy and nivolumab alone versus ipilimumab monotherapy irrespective of PD-L1 and BRAFV600 status as well as metastasis stage. Adverse events of grade 3 and above were commoner with the combination (55%) compared to either of the monotherapies alone (16.3% and 27.3% with nivolumab or ipilimumab respectively).

Similar results have been reported in NSCLC where a series of trials have tested the combination of PD1/PD-L1 inhibitors with immune checkpoint inhibitors in the advanced setting. Combination of ipilimumab with pembrolizumab (Gubens et al., 2016) and nivolumab (Hellmann et al., 2017) has resulted in objective response rates of 25% and 43%, respectively. However, these results came at the cost of increased the severity of toxicities associated with these therapeutic protocols. For instance, the incidence of grade 3 or higher toxicity (when ipilimumab was combined with pembrolizumab) increased to 49% compared to 10% with the use of the single-agent pembrolizumab (Garon et al., 2015; Gubens et al., 2016).

The combination of the CTLA-4 inhibitor tremelimumab with durvalumab in newly diagnosed NSCLC in a phase I trial was shown to have an acceptable toxicity profile and some objective responses (23%, 95% CI 9-44) both in patients with PD-L1-positive and those with PD-L1-negative tumors as well (Antonia et al., 2016a). However, the preliminary results of the phase III MYSTIC trial, reported in July 2017, were not overly encouraging for the combination of tremelimumab with durvalumab as this treatment protocol was unable to delay tumor progression longer than chemotherapy on its own. Finally, the OS results are awaited.

2.3.2. Combination of PD1/PD-L1 checkpoint inhibitors with targeted therapies

The combination of PD1/PD-L1 checkpoint inhibitors with targeted therapies is another interesting concept which is currently being investigated. A number of key observations has prompted research towards the direction of utilizing BRAF and MEK inhibitors in melanoma. Treatment with BRAF inhibitors has been associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic disease (Frederick et al., 2013) whilst resistance to BRAF inhibitor vemurafenib due to the activation of alternative signaling pathways was accompanied by the induction of PD-L1 expression (Atefi et al., 2014). In addition, MEK inhibitors stimulate the expression of microphthalmia-associated transcription factor (MITF) as well as the melanocyte-lineage antigen expression leading to augmentation of T cell infiltration (Hu-Lieskovan et al., 2015). They also interrupt the entry of effector T-cells into the tumor (Ebert et al., 2016).

Various combinations of targeted therapy and checkpoint inhibitors including triplets of BRAF, MEK inhibitors and PD-1/PDL-1 blockade agents have been or are being tested. Preliminary results from the phase I KEYNOTE 022 study, utilizing dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) with pembrolizumab in advanced melanoma showed an unconfirmed objective response rate in 15 patients of whom 60-67% experienced grade 3 (or above) toxicities (Ribas et al., 2016). In addition, in this study, the efficacy and safety of the therapeutic combination is being evaluated as first line therapy for BRAF mutant melanoma patients.

In NSCLC, early phase results of combinations of the EGFR inhibitor erlotinib with either nivolumab (Gettinger et al., 2014) or atezolizumab (Rudin et al., 2016) showed acceptable toxicity levels and promising activity. In the case of nivolumab + erlotinib, this was achieved in EGFR mutant NSCLC patients who had developed resistance to previous anti- EGFR therapy. However, in trying to establish a rationale for the combination of either EGFR or ALK inhibition with PD-1/PDL-1, available clinical evidence shows that response to PD-1/PDL-1 inhibitors is low in EGFR mutant and ALK rearranged patients compared to EGFR and ALK wild type or those with unknown status (3.6 versus 23.3%, P = 0.053) (Gainor et al., 2016). In addition, preclinical studies showed no synergistic tumor cell killing effect when EGFR inhibitors were combined with anti-PD-1 therapies. Nevertheless, a number of clinical trials designed to test the combination of an EGFR inhibitor (osimertinib) with a PD-L1 inhibitor (durvalumab) reached the clinical setting but had to be suspended in light of disappointing efficacy and toxicity results (Ahn et al., 2016; and NCT02454933).

Vascular endothelial growth factor (VEGF) inhibitors is another group of drugs that have been combined with PD1/PD-L1 axis blockade agents; the rationale being that VEGF can enhance the immunosuppressive cells, reduce the tumoral concentration of lymphocytes and suppress the dendritic cell maturation (Mahoney, Rennert, & Freeman, 2015). Nivolumab has been combined with sunitinib or pazopanib as a second-line treatment in patients with metastatic renal cancer, in a phase I study, providing promising results with both antiagiogenic agents (Amin et al., 2014). Grade 3-4 adverse events were manageable in both arms. In another phase I trial Bevacizumab a VEGFR receptor inhibitor was combined with nivolumab versus nivolumab monotherapy in advanced stage NSCLC after first-line platinum-based chemotherapy (CheckMate 012 study; Hellmann et al., 2017). Response was similar in both arms but the combination arm (including only patients with non-squamous histology) had a higher PFS but not OS rate compared to the monotherapy arm which included patients with both squamous and non-squamous histology.

Sorafenib another angiogenesis inhibitor has been shown to induce in vitro autophagy and suppress activation of tumor associated macrophages (TAMs), which associate with tumor microvessel density and VEGF levels in renal cell and hepatocellular carcinoma (Deng, Liu, Lian, Li, & Hou, 2016; Zhao, Guo, Wang, Chu, & Hu, 2017). Sunitinib may enhance the immune anticancer response by decreasing the number and effectiveness of suppressor cell (Tregs and myeloid-derived stem cells, MDSCs), which are markedly involved in the pro-angiogenic phenotype of RCC (Santoni et al., 2014; Tazzari et al., 2014). Based on these findings, the combination of PD-1/PD-L1 blocking agents with antiangiogenic drugs has been evaluated in preclinical and clinical studies.

According to results from the phase III IMpower150 trial (NCT02366143), the combination of atezolizumab with carboplatin plus paclitaxel (with or without bevacizumab) in the first line treatment of advanced non-squamous NSCLC was recently reported to improve PFS. Such combination of atezolizumab, bevacizumab and chemotherapy was superior to bevacizumab and chemotherapy alone with a median PFS of 8.3 versus 6.8 months (HR 0.62; 95% [CI] 0.52, 0.74; P < 0.0001). Moreover, patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements were excluded.

2.3.3. Combination of PD-1/PD-L1 inhibitors with chemotherapy

The rationale of combining PD-1/PD-L1 inhibitors with chemotherapy is multifactorial including evidence – primarily preclinical – showing that chemotherapy can enhance the immune response against cancer (Liu, Fowler, Smith, & Dalgleish, 2010), induce PD-L1, expression in tumor cells (Peng et al., 2015; Zhang et al., 2016) and also reduce the tumor burden thus facilitating response to checkpoint inhibitors (Melero et al., 2015). There are several examples of such combinations predominately in melanoma and lung cancer. Currently, based on the results of the KEYNOTE-021 phase II randomized trial, the only FDA approved combination is that of pembrolizumab with pemetrexed and carboplatin as first-line treatment of metastatic NSCLC, irrespective of PD-L1 expression. In this trial, the combination of pembrolizumab with chemotherapy yielded a significantly higher overall response rate compared to chemotherapy alone (55% versus 29% respectively) with an indicated difference of 26%, (95% CI 9-42%, p = 0.0016) (Langer et al., 2016). The PFS was also significantly higher (13.0 vs. 8.9 months; HR, 0.53; 95% CI, 0.31–0.91; P = 0.010) and as expected the frequency of grade 3–4 treatment-related toxicities was higher in the combination arm (39% vs 26%).

2.4. Toxicity of PD-1/PD-L1 inhibitors

The side effects related to the PD-1/PD-L1 axis inhibitors are generally considered well tolerated and manageable particularly when compared to the toxicity profile of other immunotherapy drugs such as the CTLA-4 inhibitors (Brahmer et al., 2012) and chemotherapy. In a recent meta-analysis by Nishijima, Shachar, Nyrop, and Muss (2017) on safety and tolerability of PD-1/PD-L1 inhibitor in 3,450 patients with advanced cancer, from 7 randomized controlled studies, Nivolumab, Pembrolizumab and Atezolizumab were found to have a significantly lower risk of any all-grade and high-grade adverse events (e.g. fatigue, sensory neuropathy, diarrhea and hematologic toxicities, anorexia, nausea, constipation) and treatment discontinuation compared to chemotherapy (Nishijima et al., 2017). However, there was an increased risk of all-grade rash, pruritus, colitis, hypothyroidism, hyperthyroidism, and pneumonitis with PD1/PD-L1 inhibitors. Such observations point to the need for an improved understanding and appropriate management of such immune-related toxicities induced by these agents which, in some cases, may even be detrimental. Whilst research in this field is ongoing, early recognition and treatment of grade 1–2 adverse effects is the current recommendation in order to prevent patient morbidity and mortality (Haanen et al., 2017). In addition, the use of immunosuppressive agents - essentially steroids - in the management of the side effects does not appear to compromise the checkpoint blockade efficacy (Friedman, Proverbs-Singh, & Postow, 2016; Haanen et al., 2017). Finally, selected clinical trials with PD-1 and PD-L1 checkpoint immune-inhibitors in various cancer histologies are shown in Table 2.

Table 2
Selected clinical trials with PD-1 and PD-L1 inhibitors in various cancer histologies.

Cancer type	Agent	Setting	Regimen	Phase	N	Primary outcomes	Reference
Melanoma	Nivolumab	First line	Monotherapy vs dacarbazine	III	418	1-year OS 72.9% vs 42.1% respectively	Robert, Long, et al., 2015a
		Anti CTLA-4 refractory	Monotherapy vs chemotherapy	III	405	ORR 31.7% vs 10.6% respectively	Weber et al., 2015
		First line	Monotherapy vs ipilimumab vs both	III	945	Median PFS 6.9 months vs 2.9 months vs 11.5 months respectively	Larkin et al., 2015
		First line	combination with ipilimumab vs ipilimumab	II	142	2-year OS 63.8% vs 53.6% respectively	Hodi et al., 2016
		First line	Monotherapy vs ipilimumab	III	906	12-month recurrent free survival 70.5% vs 60.8% respectively	Weber et al., 2017
	Pembrolizumab	First line	Monotherapy vs ipilimumab	III	834	OS hazard ratio 0.69 PFS hazard ratio 0.58	Robert, Schachter, et al., 2015b
		Anti CTLA-4 refractory	Monotherapy	NA	173	ORR 26%	Robert et al., 2014
		Anti CTLA-4 refractory	Monotherapy vs chemotherapy	III	540	6-month PFS 34% at 2mg/kg vs 38% at 10mg/kg vs 16% in chemotherapy	
	PDR001	First line	Combination with dabrafenib and trametinib	III	9	3 pts CR, 6 PR (prelim data)	Dummer et al., 2018
	JS001	Advanced	Monotherapy	I	22	13% ORR	Chi et al., 2017
	Atezolizumab (MPDL3280A)[a]	First line	Monotherapy	II	45	1-year ORR 26%	Hamid et al., 2013
	BMS-936559 (MDX-1105)	Second/Further line	Monotherapy	I	52	1 year ORR 6% (at 1 mg/kg), 29% (at 3mg/kg) and 19% (at 10mg/kg)	Brahmer et al., 2012
		Advanced	monotherapy	Ib	53	11%, 35%, 18% response rate at 1, 3, 10 mg.kgr respectively	Brahmer et al., 2012
NSCLC	Nivolumab	Relapsed/refractory, non-squamous	Monotherapy vs docetaxel	III	582	Median OS 12.2 months vs 9.4 months respectively	Borghaei et al., 2015
		Relapsed/refractoy, squamous	Monotherapy vs docetaxel	III	272	Median OS 9.2 months vs 6 months respectively	Brahmer et al., 2015
	Pembrolizumab	Relapsed/refractory	Monotherapy vs docetaxel	III	1034	OS Hazard ratio 0.71 (at 2mg/kg) and 0.61 (at 10mg/kg)	Herbst et al., 2016
		First line	Monotherapy vs platinum based chemotherapy	III	305	Median PFS 10.3 months vs 6 months respectively, 6-month OS 80.2% vs 72.4% respectively	Reck et al., 2016
		Second or further	monotherapy	I	495	19.4% ORR, median OS 12 months, median PFS 3.7 months	Garon et al., 2015
	Atezolizumab (MPDL3280A)	Platinum refractory	Monotherapy vs docetaxel	II	144	OS 12.6 months vs 9.7 months respectively	Fehrenbacher et al., 2016
		Second or further	Monotherapy vs docetaxel	III	1225	OS 13.8 months vs 9.6 months, HR 0.73	Rittmeyer et al., 2017
		Multiple lines	monotherapy	II	First line 139, Second line 268, third or further line 252	Median OS 23.5, 15.5 and 13.2 months respectively	Peters et al., 2017
	Durvalumab (MEDI4736)	Adjuvant to platinum based chemotherapy	Adjuvant vs placebo	III	713	Median PFS 16.8 vs 5.6 months respectively	Antonia et al., 2017
	Avelumab (MSB0010718C)	Second or further	monotherapy	Ib	184	12% had OR, 50% DCR	Planchard et al., 2016
	BMS-936559 (MDX1105)	Advanced	monotherapy	Ib	50	28% response rate at 10mg/kg	Brahmer et al., 2012
		Second/Further line	Monotherapy	I	49	1 year ORR 8% (at 3mg/kg) and 16-% (at 10mg/kg)	Brahmer et al., 2012

Table 2 (*continued*)

Cancer type	Agent	Setting	Regimen	Phase	N	Primary outcomes	Reference
RCC	Nivolumab	Anti-VEGFR refractory	Monotherapy vs everolimus	III	821	Median OS 25 vs 19.6 months respectively, ORR 25% vs 5%	Motzer et al., 2015
		First line	Nivolumab plus ipilimumab vs sunitinib	III	550 vs 546	ORR 41.6% vs 26.5% respectively, median PFS 11.6 vs 8.4 months for intermediate/poor risk	Escudier et al., 2017a
		Relapsed	Monotherapy vs everolimus	III	410 vs 411	HR 0.48 for poor risk patients	Motzer et al., 2015
		Progression with nivolumab	Nivolumab	II	153	28% had ≥30% tumor reduction	Escudier et al., 2017b
	Pembrolizumab	Relapsed	Plus Epacadostat (IDO1)	I/II	27	44% had CR/PR, DCR 81%	Lara et al., 2017; NCT02178722
	Atezolizumab (MPDL3280A)	Relapsed	monotherapy	I	70	Median OS 28.9 months, median PFS 5.6 months, ORR 15%	McDermott et al., 2016
		First line	Atezolizumab plus bevacizumab vs atezolizumab vs sunitinib. If monotheraoy failed, cross to atezolizumab plus bevacizumab	II	101 (atezo + bev), 103 (atezo), 101 (sun)	Median PFS 11.7 vs 6.1 vs 8.4 months respectively ORR 32%, vs 25% vs 29% respectively. After crossover, ORR 26%, PFS was 8.8 months	Atkins et al., 2017
		First line mRCC	Atezolizumab +/- bevacizumab vs sunitinib	II	101 (atezo +bev), 103 (atezo), 101 (Sun)	Median PFS 11.7, vs 6.1 vs 8.4 months respectively. ORR 32%, 25%, 29% respectively	McDermott et al., 2017
	Avelumab (MSB0010718C)	First line	Avelumab plus axitinib	Ib	55	ORR 54.5%	NCT02493751, Choueiri et al., 2017
	BMS-936559 (MDX1105)	Second/Further line	Monotherapy	I	17	12% at 10mg/kg	Brahmer et al., 2012
Urothelial cancer	Nivolumab	Locally advanced/metastatic after platinum-based therapy	monotherapy	I/II	86	OR 24.4%, median PFS 2.8 months, 1-year OS 51.6%	NCT01928394, CheckMate 032, Sharma et al., 2016
		Metastatic after platinum-based therapy	monotherapy	II	270	ORR 19.6%	NCT02387996, CheckMate275, Sharma et al., 2017
		Refractory metastatic	Nivolumab + cabozantinib +/- ipilimumab	I	19	ORR 44% vs 29% respectively	NCT02496208, Apolo et al., 2017a
	Pembrolizumab (MK-3475, Lambrolizumab)	First line Cisplatin-ineligible, advanced	Monotherapy	II	374	OR 24%, 6-month OS 67%, 6-month PFS 31%	KEYNOTE-052, Balar et al., 2017a
		Platinum refractory advanced UC	Monotherapy vs chemotherapy (paclitaxel, docetaxel or vinflunine)	III	542	Median OS 10.3 vs 7.4 months, HR 0.73, Elevated PD-L1 levels have worse responses to chemo and PD-L1 inhibitors	KEYNOTE-045, Bellmunt et al., 2017
		Platinum refractory, advanced UC	Epacadostat (IDO1) plus Pembrolizumab	I/II	40	ORR 35%, DCR 57%	Preliminary results of ECHO-202/KEYNOTE-037 NCT02178722, Smith et al., 2017
	BGB-A317	Second or further	monotherapy	Ia/b	15	ORR 27%, DCR 53%	NCT02407990, Sandhu et al., 2018)
	Atezolizumab (MPDL3280A)	Second or further, platinum treated	monotherapy	II	218	ORR 16%, DCR 49%	Pal et al., 2018
		Second or further, platinum treated	monotherapy	I	97	Median PFS 2.7 months, Median OS 10.1 months, ORR 26%. 3-year OS 27%	Petrylak et al., 2018
		Platinum refractory	Monotherapy vs chemotherapy	III	931 (467 vs 464)	Median OS 11.1 vs 10.6 months, HR 0.87, ORR 23% vs 22%	IMvigor211, Powles et al., 2018
		Platinum refractory	monotherapy	II	315	ORR 15% overall, IC2/3: 27% IC1/2/3: 18%	IMvigor210, NCT02108652, Rosenberg et al., 2016
		Platinum refractory,	Atezolizumab vs	II	137	3.6% responded.	IMvigor210, Necchi et al.,

(*continued on next page*)

Table 2 (*continued*)

Cancer type	Agent	Setting	Regimen	Phase	N	Primary outcomes	Reference
		progression after atezolizumab	other treatment vs no treatment			Median OS 8.6 vs 6.8 vs 1.2 months	2017
		First line, platinum ineligible	Monotherapy	II	119	ORR 23%, Median PFS 2.7 months, median OS 15.9 months	Balar et al., 2017a,b
	Durvalumab (MEDI4736)	Second line	Monotherapy	I/II	191	ORR 17.8%, median PFS 1.5 months, median OS 18.2 months, 1-year OS 55%	Powles et al., 2017
	Avelumab (MSB0010718C)	Platinum refractory, metastatic	Monotherapy	I	249	ORR 17%, DCR 40%, median PFS 1.6 months, median OS 6.5 months	JAVELIN Solid Tumor, Patel et al., 2018
		Platinum refractory, metastatic	Monotherapy	Ib	44	ORR 18.2%, median PFS 2.9 months, median OS 13.7 months, 1-year OS 54.3%	Apolo et al., 2017b
SCLC	Nivolumab	Platinum refractory, Recurrent	Nivolumab vs nivolumab plus ipilimumab	I/II	216	ORR 10%at nivo 3mg/kg vs 33% (at nivo 1mg/kg and ipi 1mg/kg), 23% (at nivo 1mg/kg and ipi at 3 mg/kg), 19% (at nivo 3mg/kg and ipi at 1mg/kg)	Antonia et al., 2016b
	Pembrolizumab	Extensive stage (ES)	Monotherapy	Ib	24	ORR 33%	KEYNOTE-028, Ott et al., 2017a
		ES	Maintenance monotherapy to initial chemotherapy	II	45	DCR 42.2%, median PFS 1.4 months, median OS 9.2 months	NCT02359019, Gadgeel et al., 2017
Mesothelioma	Nivolumab	Progressive disease	monotherapy	II	34	ORR 14.7%, DCR 50%	Quispel-Janssen et al., 2017
		Progressive disease, second or third line	monotherapy	II	34	6-month ORR 29.4%, 6-month DCR 67.6%, 6-month PFS 50.9%, 6-month OS 85.3%	MERIT, Goto et al., 2017
		Second or third line	Nivolumab versus nivolumab plus ipilimumab	II	125	ORR 16.7 vs 25.9% respectively	IFCT-1501 MAPS2, Scherpereel et al., 2017
	Pembrolizumab	Second or further line	monotherapy	Ib	25	ORR 20%, DCR 52%	KEYNOTE-028, Alley et al., 2017
		Second or third line	monotherapy	II	35	ORR 21%, DCR 77%, median PFS 6.2 months	NCT02399371, Kindler et al., 2017
	Durvalumab	First or Second line	Tremelimumab plus durvalumab	II	40	ORR 25%, DCR 62.5%	NIBIT-MESO-1, Calabro et al., 2017
	Avelumab	Second or further line	Monotherapy	Ib			JAVELIN, Hassan et al., 2016
HNSCC	Nivolumab	Recurrent, after platinum based treatment	Monotherapy vs standard chemotherapy (methotrexate, docetaxel or cetuximab)	III	361	Median OS 7.5 vs 5.1 months, (HR 0.7), median PFS 2 vs 2.3 months, ORR 13.3% vs 5.8%	CheckMate141, Ferris et al., 2016
	Pembrolizumab	Platinum/cetuximab refractory	Monotherapy	II	171	ORR 16%, median PFS 2.1 months, median OS 8 months	KEYNOTE-055, Bauml et al., 2017
		Recurrent/metastatic	Monotherapy	Ib	104	ORR 18%(25% in HPV+ vs 14% in HPV-)	KEYNOTE-012, Seiwert et al., 2016
	Tislelizumab (BGB-A317)	Relapsed	monotherapy	I	18	ORR 5%, DCR 50%	NCT02407990, Horvath et al., 2017
	Atezolizumab	Second or further line	Monotherapy	Ia	32	ORR 22%, median PFS 2.6 months, median OS 60months	Balheda et al., 2017
	Durvalumab	Second or further line	Monotherapy	II	112	ORR 13.5%(26.5% in HPV+ vs 7.9% in HPV-), Median PFS 2.3 months	Zandberg et al., 2017

Table 2 (*continued*)

Cancer type	Agent	Setting	Regimen	Phase	N	Primary outcomes	Reference
Nasopharyngeal	Nivolumab	Recurrent/metastatic	Monotherapy	I/II	24	ORR 20.8%, DCR 45.8%, median PFS 2.4 months	CheckMate 358, Delord et al., 2017
	Pembrolizumab	Second or further line	Monotherapy	I/b	27	ORR 25.9%, DCR 77.8%	KEYNOTE-028 (NCT02054806) Hsu et al., 2017
Esophageal/Gastric cancer	Nivolumab	Refractory EC	Monotherapy	II	65	ORR 17%	ONO-4538-07, Kudo et al., 2017
		Second or further line GEJ cancer	Monotherapy salvage vs placebo	III	439	Median OS 5.32 vs 4.14 months, ORR 11.2% vs 0%, median PFS 1.61 vs 1.45 months	NCT02267343, ONO-4538-12 Kang et al., 2017
		Third or further, gastric, EC, GEJ	Nivolumab +/- ipilimumab	III	160 (doses N3, 59; N1-I3, 49; N3-I1, 52)	ORR 12%, 24%, 8% respectively, median OS 6.2, 6.9, 4.8 months respectively	CheckMate 032, NCT01928394 Janjigian et al., 2017
	Pembrolizumab	Third or further line, Recurrent/metastatic gastric/GEJ	Monotherapy	Ib	36	ORR 22%, DCR 36% Median PFS 1.9 months, median OS 11.4 months	KEYNOTE 012, Muro et al., 2016
		Second line or further, EC/GEJ	Monotherapy	Ib	23	ORR 30%, DCR 43%, 6-month PFS 30%, 12-month PFS 22%	KEYNOTE-028, Doi et al., 2016
		Third line or further, gastric/EC	monotherapy	II	259(Cohort 1)	ORR 60%, median PFS 2 months, median OS 6 months	KEYNOTE-059, Fuchs et al., 2017
		First line	Combination with cisplatin plus 5-FU or capecitabine	II	25(Cohort 2)	ORR 60%, median PFS 7 months, Median OS 14 months	KEYNOTE-059, Wainberg et al., 2017; Bang et al., 2017
		First line	Monotherapy	II	31(Cohort 3)	ORR 26.2%, median PFS 3.3 months, 6-month OS 73%, 12-month OS 62%	KEYNOTE-059, Weinberg et al., 2017; Catenacci et al., 2017
		Second or further line, gastric/EC	Pembro plus Ramucirumab (VEGFR2)	Ia/b	40	ORR 7.5%, DCR 45%, Median PFS 2.6 months at ramucirumab 10mg/kg	Chau et al., 2017
	JS001	Third or further line, refractory gastric	Monotherapy	Ib/II	48	ORR 20% (60% in PD-L1+), DCR 60% (80% in PD-L1+)	NCT02915432, Xu et al., 2018
	Tislelizumab (BGB-A317)	Second or further line, gastric/EC	Monotherapy	I/II	55	ORR 5.7%, DCR 32%	NCT02407990, Desai et al., 2017
	Camrelizumab (INCSHR-1210; SHR-1210)	Multiple histologies	monotherapy	I	37	ORR 35.1%	NCT02742935, Huang et al., 2017
	Avelumab	First or second line, gastric/GEJ	monotherapy	Ib	151 (maintenance in first line, 89; second line 62)	ORR 9%, 9.7% respectively, DCR 57.3%, 29% respectively, median PFS 3 and 1.5 months respectively	NCT01772004, Chung et al., 2016
		Relapsed gastric/GEJ	Monotherapy	I/II	20	ORR 15% (40% in PD-L+), DCR 65%, median PFS 3.1 months	NCT01943461, Nishina et al., 2016
	M-7824 (MSB-0011359-C)	Fourth line or greater Recurrent/refractory gastric	Monotherapy	I	31	ORR 16.1%	NCT02699515, Kang et al., 2018
CRC	Nivolumab	Metastatic mismatch repair deficient or microsatellite instability high	Monotherapy, fourth line or greater	II	74	ORR 31.1%, DCR 69%, 1-year OS 73%	CheckMate 142, Overman et al., 2016b
		Metastatic mismatch repair deficient or microsatellite instability high	Nivolumab plus ipilimumab followed by nivolumab,	II	119	ORR 55%, 80% had DCR ≥3 months, 12-month PFS 71%, 12-month OS 85%	CheckMate 142, Overman, Kopetz, et al., 2016b, Overman et al., 2017
		Refractory MSI high	Nivolumab +/- ipilimumab		47 (monotherapy), 30 (combination)	ORR 56% vs 33% respectively	Overman et al., 2018
	Pembrolizumab	Refractory/relapsed	Monotherapy regardless of MSI	Ib	137, (PD-L1 +, 23)	ORR 4% (MSI high)	KEYNOTE -028, O'Neil et al., 2017

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Table 2 (*continued*)

Cancer type	Agent	Setting	Regimen	Phase	N	Primary outcomes	Reference
			status				
		Refractory/relapsed	Monotherapy regardless of MSI status	II	32 (11, MSIhigh; 21, MSI low)	ORR 40%, 0% respectively, PFS 78% and 11% respectively, median PFS NR vs 2.2 months respectively, median OS NR vs 5 months respectively	Le et al., 2015
		Refractory/relapsed, Metastatic mismatch repair deficient or microsatellite instability high	Monotherapy in MSI high	II	40 patients with colorectal cancer, 46 with other MSI high histologies	ORR 52%, DCR 82%, 2-year PFS 59%, 2-year OS 72% for CRC patients	Le et al., 2017
		Metastatic mismatch repair deficient or microsatellite instability high	Monotherapy, Third or further line	II	61	ORR 26.2%, DCR 50.8%	KEYNOTE 164
		Relapsed regardless of MSI status	mFOLFOX6 plus pembrolizumab	II	30	ORR 53%, early results	NCT02375672, Shahda et al., 2017
	AMP-224	Metastatic to liver	Plus stereotactic body radiation therapy (8gy, DL1 in one fraction or Dl2 in 3 fractions)	I	17 (8, DL1; 9, DL2)	0% ORR	NCT02298946, Duffy et al., 2016
	Atezolizumab (MPDL3280A)	MSI high metastatic CR	Atezolizumab plus bevacizumab vs atezolizumab plaus bevacizumab plus chemotherapy (FOLFOX)	Ib	14 vs 30	ORR 7% vs 40%,	GP28328 study, NCT01633970 Bendell et al., 2015
		Recurrent mCRC, third line or further	Atezolizumab plus cobimetinib (MEK inhibitor)	Ib	84	Median OS 9.8 months, 12-month OS 43%, ORR 0.7%, median PFS 1.9 months, 6-month PFS 18%	GP 28363, NCT01988896, Bendell et al., 2018
		Locally advanced, metastatic CEA+ CRC	Atezolizumab plus RO6958688 (CEA and CD3e T-cell antibody)	Ib	35	ORR 12%, DCR 52%	NCT02650713, WP29945 study, Tabernero et al., 2017
	BMS-936559 (MDX1105)	Second/Further line	monotherapy	I	18	No responses	Brahmer et al., 2012
Anal canal	Nivolumab	Refractory/relapsed unresectable metastatic	monotherapy	II	37	24% ORR	NCI9673, Morris et al., 2017
	Pembrolizumab	Recurrent/relapsed	monotherapy	Ib	25	17% ORR, DCR 27%	KEYNOTE-028, Ott et al., 2017b
Pancreatic	Nivolumab	Locally advanced, metastatic, first (arm b) or second line (arm a)	Nivolumab plus nab-paclitaxel +/- gemcitabine	I	11 (arm a), 6 (arm b)	ORR 18% vs 50 % respectively, DCR 36.4% vs 50% respectively	NCT02309177, Weinberg et al., 2017
	Pembrolizumab	relapsed metastatic	REOLYSIN (reovirus) plus pembrolizumab plus chemotherapy	II	11	ORR 9%, DCR 27.3%	NCT02620423, Mahalingam et al., 2017
		Metastatic	Gemcitabine plus nab-paclitexel plus pembrolizumab	Ib/II	17 (11 chemo naïve)	For chemo naïve patients: ORR 17.6%, DCR 100%, median PFS 9.1 months, median OS 15 months	NCT02331251, Weiss et al., 2018
		Metastatic, second or further line	Acalabrutinib (BTK inhibitor) +/- pembrolizumab	II	44 (21 monotherapy vs 23 combination)	ORR 0% vs 13% respectively, DCR 19% vs 24.7%	NCT02362048, Overman et al., 2016a
NET	Pembrolizumab	Advanced carcinoids (lung, gut, other) pancreatic NET, PNET	Monotherapy	Ib	41, 25 carcinoids (lung, 9; gut, 7; other 9) vs 16 PNETs	ORR 12% vs 6%, DCR 72% vs 94%	NCT02054806, KEYNOTE-028, Mehnert, Rugo, O'Neil, Santoro, & Piha-Paul, 2017
HCC	Nivolumab	Second line after sorafenib	monotherapy	I/II	262	ORR 20% (at 3mg/kg dose expansion), 15% (dose escalation) in sorafenib naïve, ORR was 23%, DCR 64%. In sorafenib	CheckMate040, El-Khoueiry et al., 2017; Crocenzi et al., 2017

Table 2 (*continued*)

Cancer type	Agent	Setting	Regimen	Phase	N	Primary outcomes	Reference
						pretreated, ORR was 16-19%	
	Durvalumab (MEDI4736)	Unresectable, sorafenib resistant or intolerant	Durvalumab plus tremelimumab (CTLA-4)	I/II	40	ORR 15%, DCR ≥16 weeks, 57.5%	NCT02519348, Kelley et al., 2017
Endometrial carcinoma	Nivolumab	MSI high, heavily pretreatedrelapsed/refractory	monotherapy	Case series	2	Both responded	Santin et al., 2016
	Pembrolizumab	Second or further line	monotherapy	Ib	24	ORR 13%, 6-month PFS 19%, 6-month OS 68.8%	KEYNOTE-028, Ott et al., 2017c
		Second or further line	Plus lenvatinib (MTKI)	Ib/II	23	ORR 48%, DCR 96%	NCT02501096, Makker et al., 2017
	Atezolizumab	Advanced	monotherapy	Ia	15	ORR 13%, DCR 27%, median PFS 1.7 months, median OS 9.6 months	NCT01375842, Fleming et al., 2017
Cervical/vaginal/vulvar cancer	Nivolumab	Recurrent/metastatic cervical/vaginal/vulvar cancer	monotherapy	I/II	24 (19, 5, 5 respectively)	ORR 20.8% (all cervical cancer), DCR 70.8%, median PFS 5.5 months	NCT02488759, CheckMate-358, Hollebecque et al., 2017
	Pembrollizumab	Second or further line, advanced cervical carcinoma	monotherapy	Ib	24	ORR 17%, DCR 30%, median PFS 2 months, median OS 11 moonths	NCT02054806, KEYNOTE-028, Frenel et al., 2017
		Second or further line advanced cervical carcinoma	monotherapy	II	47	ORR 17%	NCT02628067, KEYNOTE-158
Uterine leiomyo-sarcoma	Nivolumab	metastatic	monotherapy	II	12	O% ORR, median PFS 1.8 months	Ben-Ami et al., 2017
Ovarian cancer	Nivolumab	Platinum-resistant	Monotherapy	II	20	ORR 15%, DCR 45%, median PFS 3.5 months, median OS 20 months	Hamanishi et al., 2015
	Pembrolizumab	Advanced, Second-line or further	Monotherapy	Ib	26	ORR 11.5%, DCR 24.6%, median PFS 1.9 months, median OS 13.1 months	NCT02054806, KEYNOTE-028, Varga et al., 2017
	Tislelizumab (BGB-A317)	Recurrent/refractory	monotherapy	I	51	ORR 3.9%, DCR 43%	NCT02407990, Meniawy et al., 2017
	Avelumab	recurrent/refractory, second or further line	monotherapy	Ib	124	ORR 9.7% (12.3% in PD-L1+ vs 5.9% in PD-L1-), DCR 54%, median PFS 2.8 months, median OS 10.8 months	NCT01772004, JAVELIN Solid Tumor, Disis et al., 2016
	BMS-936559 (MDX1105)	Second/further line	monotherapy	I	17	ORR 6%, DCR 24%, 6-month PFS 22%	NCT00729664, Brahmer et al., 2012
Breast cancer	Nivolumab	Metastatic TNBC, fourth line or less	Monotherapy after chemotherapy induction	II	50	ORR 22%, DCR 26%	TONIC-trial, Kok et al., 2017
	Pembrolizumab	Metastatic TNBC, second line or further	Monotherapy	Ib	27	ORR 18.5%, DCR 44.4%, 6-month PFS 24.4%	KEYNOTE-012, NCT01848834, Nanda et al., 2016
		Neoadjuvant, HER2-	Paclitaxel, doxorubicin, cyclophosphamide plus pembrolizumab	II	25 (HR +/HER2-) vs 21 (TNBC)	pCR 28% vs 71.4%	I-SPY 2. NCT01042379, Nanda et al., 2017b
	Atezolizumab	Metastatic TNBC, many lines, fourth line or less	Atezolizumab plus nab-paclitaxel	Ib	24	ORR 42%, DCR 63%	NCT01633970, Adams et al., 2016
	Durvalumab (MEDI4736)	Metastatic	durvalumab plus tremelimumab (CTLA-4 inhibitor)	II	18 (11 ER+; 7 TNBC)	ORR 16.7% (0% ER+; 43% TNBC) DCR 23.5% (0% ER+; 57.1% TNBC)	NCT02536794, Santa-Maria et al., 2017
	Avelumab	Locally advanced/metastatic, second/further line	Monotherapy	Ib	168 (58 TNBC)	ORR 3% (5.2% in TNBC)	JAVELIN Solid Tumor; NCT01772004, Dirix et al., 2018
Thyroid	Pembrolizumab	Advanced papillary/follicular, third line or further	Monotherapy	Ib	22	ORR 9.1%, DCR 63.6%, 6-month PFS 58.7%, 6-month OS 100%	KEYNOTE-028; NCT02054806,
Sarcoma	Nivolumab	Advanced, metastatic, unresectable	Nivolumab +/- ipilimumab	II	76 (38 nivo, 38 nivo+ ipi)	ORR 5% and 16% respectively	Alliance A091401, NCT02500797, D'Angelo et al., 2018
	Pembrolizumab	advanced soft tissue (STS) and bone sarcomas (BS)	Monotherapy	II	84 (40 STS, 40 BS)	ORR (18% STS; 5% BS),	SARC028, NCT02301039, Tawbi et al., 2017; Burgess et al., 2017

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Table 2 (*continued*)

Cancer type	Agent	Setting	Regimen	Phase	N	Primary outcomes	Reference
Cutaneous SCC	REGN-2810 (SAR-439684)	unresectable locally advanced or metastatic	Monotherapy	I	26	ORR 52%, DCR 70%	NCT02383212, Papadopoulos et al., 2017
Merkel cell carcinoma	Nivolumab	Refractory, First/further line	Monotherapy	I	22	ORR 71%, 3-month PFS 82%, 3-month OS 92%	CheckMate 358, Topalian et al., 2017
	Pembrolizumab	Refractory, First line	monotherapy	II	25	ORR 56%, 6-month PFS 67%, 9-month PFS 56%	Nghiem et al., 2016
	Avelumab	Refractory, Second/further line	Monotherapy	II	88	ORR 31.8%, median PFS 2.7 months	Kaufman et al., 2016
Adreno-cortical carcinoma	Nivolumab	Metastatic/locally advanced, secon/furhter line	Monotherapy	I	7	ORR 0%, early results	NCT02720484
	Avelumab	Relapsed, previous mitotetane	Monotherapy	Ib	37	ORR 10.5%, DCR 36.8%, Median PFS 1.9 months, 3-month PFS was 30.3%	JAVELIN, NCT01772004, Tourneau et al., 2016
Hodgkin's lymphoma	Nivolumab	Relapsed/refractory	Monotherapy	I	23	ORR 87%, 6-month PFD 86%	Ansell et al., 2015
		Relapsed/refractory	brentuximab vedotin (BV) and nivolumab (Nivo)	I/II	62	ORR 82%	NCT02572167, Herrera et al., 2017
	Pembrolizumab	Relapsed/refractory	Monotherapy	II	210	ORR 69%, CR 22.4%	NCT02453594, KEYNOTE-087, Chen et al., 2017
		Relapsed/refractory after Brentuximab vedotin	Monotherapy	Ib	31	ORR 65%, CR 16%, 6-month PFS 69%, 1-year PFS 46%	KEYNOTE-013, NCT01953692, Armand et al., 2016
NHL	Nivolumab	Relapsed/refractory	Monotherapy	Ib	81 (10 follicular lymphomal 11 DLBCL; 13 mycosis fungoides; peripheral T-cell 5; multiple myeloma 27)	ORR 40%, 36%, 15%, 40%, 4% respectively; DCR 100%, 63%, 84%, 40%, 67% respectively	Lesokhin et al., 2016
NHL: NK/T-cell lymphoma	Pembrolizumab	relapsed/refractory after l-asparaginase	Monotherapy	I	7	5 CR	Kwong et al., 2017
		relapsed/refractory	monotherapy	I	7	ORR 57%, 2 CR	Li et al., 2018
Multiple myeloma	Pidilizumab (CT-011)	Relapsed/Refractory, second/further line	Lenalidomide plus CT-011	I/II	12	1 PR, 3 VGPR	Efebera et al., 2015
	Nivolumab	Relapsed/refractory	Monotherapy	Ib	27	ORR 4%, DCR 67%	Lesokhin et al., 2016
	Pembrolizumab	relapsed/refractory, third/further	Pembrolizumab, pomalidomide, and low-dose dexamethasone	II	48	ORR 60%, CR 8%, VGPR 19 %, PR 33%	Badros et al., 2017

BS, bone sarcoma; CEA, carcinoembryonic enzyme; CR, complete response; DCR, disease control rate; DLBCL, diffuse large B-cell lymphoma; EC, esophageal cancer; ES-extensive stage; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; IC, tumor infiltrating cells; IDO1, Indoleamine 2,3-dioxygenase; MMR, mismatch repair; mRCC, metastatic renal cell carcinoma; MSI, microsatellite instability; NET, neuroendocrine tumor; NHL, non Hodgkin's lymphoma; NK, Natural killer; NSCLC, non small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; STS, soft tissue sarcoma; VEGFR, vascular endothelial growth factor receptor; VGPR, very good partial response.

[a] crossover to atezolizumab plus bevacizumab was allowed if progression occurred with atezolizumab alone or sunitinib alone.

3. Challenges

Although the fast development and subsequent introduction of immunotherapy agents in the management of different malignancies, a number of issues remain in relation to their toxicity profile, the role of predictive biomarkers and the financial burden they are associated.

The cost of immunotherapy drugs is high and the increasing number of applications in cancer can only increase the financial burden to society. One of the concerning issues with regards to clinical trials leading to approval of PD1/PDL-1 inhibitors is that encouraging results in terms of PFS and OS from phase II studies have not been confirmed, as yet, in phase III studies. Such examples include the CheckMate 026 and the KEYNOTE 040 trials (Carbone et al., 2017; Cohen et al., 2017). A number of reasons may be responsible including patient selection, variability of biomarker (PD-L1) assays used, and type of therapy used (after the completion of the phase II trial including immunotherapy in the previously standard of care arm). In any case, such results challenge the validity of the original hypotheses particularly when combinations are investigated which pose a problem for FDA-labeled indications that are based on phase II or earlier phase studies.

Combination of PD1-PDL-1 inhibitors with other agents aims to improve efficacy by taking advantage of the complementary action of these agents with other immunomodulatory drugs, targeted therapy or chemotherapy. In some cases, whilst such efficacy is enhanced, toxicity levels are unacceptable highlighting the need to consider adjustments in doses, schedule or type of combinations in order to achieve the optimal therapeutic regimen (Melero et al., 2015).

Another challenge is how to prioritize checkpoint inhibitors given that in some cases two or three agents are approved with the same indication (i.e. second line therapy for advanced/metastatic lung cancer). Currently, there is no algorithm as to which one to use over another. At present, there are no head to head efficacy comparisons and no major

Table 3
Selected investigative uses and clinical trials of anti-PD-1/PD-L1 Mabs.

Target	Molecule	Regimen/Combination with (target)	Used in	Reference	Phase
PD-1	Nivolumab (BMS-936558, MDX1106, ONO4538)	BMS-986016 (LAG3)	Solid tumors	NCT01968109	I/II
		Enoblituzumab (B7-H3)	Solid tumors	NCT02817633	I
		Lirilumab (KIR)	Solid tumors	NCT01714739	I/II
		Urelumab (4-1BB)	Solid tumors, B-NHL	NCT02253992	I/II
		JTX-2011 (ICOS)	Solid tumors	NCT02904226	I/II
		Varilumab (CD27)	Solid tumors	NCT02335918	I/II
		GM.CD40L vaccine	NSCLC	NCT02466568	I/II
		Nivolumab vs Nivolumab plus ipilimumab vs placebo	Extensive stage SCLC	CheckMate 451, NCT02538666	III
		Adjuvant perioperative nivolumab vs observation	Localized RCC, perioperative	PROSPER, NCT03055013	III
		Cisplatin and gemcitabine	Neoadjuvant for bladder cancer	NCT03294304	II
		Nivolumab plus ipilimumab or standard of care vs standard of care	Unresectable/metastatic urothelial cancer	CheckMate 901, NCT03036098	IIII
		Vs placebo	Resected lower esophageal or gastroesophageal junction cancer	CheckMate 577, NCT02743494.	IIII
	Pidilizumab (CT-011)	With DC/RCC fusion cell vaccine	mRCC	NCT01441765	II
	Pembrolizumab (MK-3475,Lambrolizumab)	Enoblituzumab (B7-H3)	Solid tumors, HNSCC, NSCLC, Urothelial, melanoma	NCT02475213	I
		Sunitinib (TKI), SBRT	TKI refractory RCC	NCT02599779	II
		Lenvatinib plus everolimus or pembrolizumab vs sunitinib	mRCC	NCT02811861.	III
		Plus axitinib versus sunitinib	First line advanced/mRCC	NCT02853331, KEYNOTE-426	III
		Plus Epacadostat (INCB024360;IDO1)	Solid tumors	NCT02178722 (KEYNOTE-137/ECHO-202)	I/II
		Monotherapy	Neoadjuvant RCC	NCT02212730	I
		Plus PF-05082566 mAb (4–1BB)	Solid tumors	NCT02179918	I
		Plus pazopanib	First line advanced RCC	NCT02014636	I/II
		Plus ipilimumab or IFN-a	RCC or melanoma	NCT02089685	I/II
		+/- chemotherapy vs chemotherapy alone	Advanced urothelial cancer	KEYNOTE-361, NCT02853305.	III
		BCG	High-risk NMIBC postsurgery	NCT02324582 (MARC)	I
		BCG	High-risk BCG-refractory NMIBC	NCT02808143	I
		Plus chemoradiotherapy	Neoadjuvant, MIBC prior to cystectomy.	NCT02736266 (PURE01)	II
		BBI608 (STAT3-WNT/βCatenin	Metastatic colorectal cancer	SCOOP study, EPOC1503, NCT02851004	I/II
		Vs investigator choice chemotherapy	mismatch repair-deficient or microsatellite instability-high metastatic colorectal carcinoma	KEYNOTE 177, NCT02563002.	III
		Vs BSC	Second line, advanced hepatocellular carcinoma	KEYNOTE-240, NCT02702401	III
	PDR001	GWN323 (GITR)	Solid tumors, lymphomas	NCT02740270	I
		monotherapy	Recurrent/metastatic nasopharyngeal carcinoma	NCT02605967	II
	AMP-514 (MEDI-0680)	Plus Durvalumab vs nivolumab monotherapy	RCC	NCT02118337	I/II
	AMP-224	Plus stereotactic body irradiation	Metastatic colorectal cancer	NCT02298946	I
	JS001	Plus axitinib	RCC, melanoma	NCT03086174	I
	BGB-A317	Plus BGB-A333 (PD-L1)	Solid tumors	NCT03379259	I/II
	IBI-308	+/- cisplatinum, pemetrexed	Solid tumors	NCT02937116	I
	REGN-2810 (SAR-439684)	Pexa-Vec (Recombinant Vaccinia virus)	mRCC	NCT03294083	Ib
		REGN2810 or investigator's choice chemotherapy	recurrent or metastatic platinum-refractory cervical cancer	NCT03257267	III
		EGN 2810 Compared to Platinum-Based Chemotherapies	advanced or metastatic NSCLC	NCT03088540	III
	Genolimzumab (GB-226)	Monotherapy	Advanced/recurrent solid tumor, lymphomas	NCT03374007	I
	Camrelizumab (INCSHR-1210; SHR-1210)	Monotherapy	Advanced hepatocellular carcinoma	NCT02989922	III/III
	CA-170 (AUPM-170)[a]	Monotherapy	Advanced tumors, lymphomas	CA-170 (AUPM-170)a	I
	PF-06801591	Monotherapy	Melanoma, Head And Neck Cancer (SCCHN), Ovarian, Sarcoma, Non-Small Cell Lung Cancer, Urothelial Carcinoma or Other Solid Tumors	NCT02573259	I
	TSR-042	Monotherapy	Advanced, metastatic solid tumors	TSR-042	I
PD-L1	Atezolizumab (MPDL3280A)	Cediranib (VEGF)	Ovarian cancer	NCT02659384	
		Varilumab (CD27)	Solid tumors	NCT02543645	
		Plus bevacizumab vs sunitinib	First line in mRCC	NCT01984242	II
		Cobimetinib (MEK)	Solid tumors, RCC	NCT01988896	I
		combination carboplatin and etoposide (PE) vs PE alone	ES-SCLC, adjuvant to first line	IMpower133 NCT02763579	
		Plus ipilimumab or IFN-a	RCC or melanoma	NCT02174172	I
		Adjuvant vs placebo	RCC with high risk post-resection	NCT03024996	III
	Durvalumab (MEDI4736)	Osimertinib (EGFR)	NSCLC	Ahn et al., 2016	
		MEDI6383 (OX40)	Solid tumors	NCT02221960	
		Olaparib (PARP) +/- Cediranib (VEGF)	Solid tumors	NCT02484404	

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Table 3 (*continued*)

Target	Molecule	Regimen/Combination with (target)	Used in	Reference	Phase
		MEDI0680 (PD-1)	Solid tumors, RCC	NCT02118337	I
		+/- Tremelimumab (CTLA-4) +platinum based chemotherapy vs chemotherapy alone	ED-SCLC	CASPIAN, CT03043872	III
		Tremelimumab (CTLA-4)	Solid tumors, RCC	NCT01975831	I
		+/- Tremelimumab (CTLA-4) vs chemotherapy	Unresectable stage IV UC	DANUBE, NCT02516241	III
		Monotherapy	Advanced endometrial cancer	PHAEDRA	II
		+/- Tremelimumab (CTLA-4)	Advanced endometrial cancer	NCT03015129	
		+/- Tremelimumab (CTLA-4)	Metastatic pancreatic ductal adenocarcinoma	NCT02558894	II
	Avelumab (MSB0010718C)	Axitinib or sunitinib	First line advanced RCC	JAVELIN Renal 101, NCT02684006	III
		Plus chemoradiotherapy (CRT) vs CRT alone	First line locally advanced HNSCC	JAVELIN head and neck 100, NCT02952586	
		Maintenance vs first line chemotherapy continuation	Advanced gastric/gastroesophageal junction	JAVELIN Gastric 100, NCT02625610	III
		Monotherapy	MSI/MSS POLE-mutated recurrent/persisted endometrial carcinoma or carcinosarcoma	NCT02912572	II
	M-7824 (MSB-0011359-C)	Plus gemcitabine	Advanced pancreatic adenocarcinoma	NCT03451773	I/II
	LY-3300054	Alone or with ramucirumab, abemaciclib, merestinib	Solid tumors, MSI high tumirs, melanoma, pancreatic cancer, HER2- breast cancer	NCT02791334	I
	SHR-1316	Monotherapy	Advanced solid tumors	NCT03133247	I
	KN035	Monotherapy	Advanced, metastatic solid tumors	NCT02827968	I

BCG: Bacillus Calmette–Guérin; BSC, best supportive care; EC, esophageal cancer; EGFR, epidermal growth factor; ES-extensive stage; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; IDO1, Indoleamine 2,3-dioxygenase; IFN-a, interferon-alpha; MEK, mitogen-activated protein kinase kinase enzyme; MIBC, muscle invasive bladder cancer; MMR, mismatch repair; mRCC, metastatic renal cell carcinoma; MSI, microsatellite instability; MSS, microsatellite stable; NET, neuroendocrine tumor; NMIBC, non muscle invasive bladder cancer; NSCLC, non small cell lung cancer; PARP, Poly (ADP-ribose) polymerase; PE, platinum-etoposide combination; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; STS, soft tissue sarcoma; UC, urothelial cancer; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

toxicity differences, perhaps with the exception of pneumonitis (and perhaps other immune-related adverse events) with anti-PD-L1 (Pillai et al., 2018) but the long term complications of these agents is yet to be defined. Finally, selected investigative uses and ongoing clinical trials of anti-PD-1/PD-L1 Mabs are presented in Table 3.

3.1. Biomarkers of response – current and emerging

The need to identify predictive biomarkers arises from the fact that checkpoint inhibitors are not effective in all patients. Instead, they can be associated with significant and unpredictable toxicity and they are costly. Therefore, it is imperative to offer such therapeutic means to those patients who are more likely to respond and also to ensure that those patients who wil not benefit can discontinue such therapy as early as possible. To date, no biomarker has been shown to have definite predictive value but the most widely used (and the only FDA approved one) is PD-L1 expression. This is justified by the fact that PD-L1 is the direct ligand to PD-1 – therefore the target of PD-1 and PD-L1 inhibitors. In a pooled analysis of 7 studies, NSCLC patients with PD-L1 tumor cell proportion score of over 1% had a significantly higher overall response rate compared to patients with PD-L1-negative tumors (OR 2.44; 95% CI 1.61-3.68) demonstrating the predictive value of this biomarker (Passiglia et al., 2016). However, a number of issues regarding the role of PD-L1 as a biomarker remain unresolved including the optimal assay to be used, the appropriate type of tissue to be used (fresh versus FFPE), the definition of PD-L1 positivity (proportion score of immune cells versus stromal cells versus tumor cells) and the dynamic nature of PD-L1 and its utility in different tumor types.

In all studies published to date (where they evaluate different checkpoint inhibitors) there has been a variation in the PD-L1 assays used for testing each inhibitor and there is also variability in the definition of PD-L1 positivity. For example, the PD-1 22C3 pharm Dx (Dako) immunohistochemical (IHC) assay is used for pembrolizumab in advanced NSCLC. This provides an assessment of membranous staining of PD-L1 on tumor cells, with a tumor proportion score (TPS) < 1% scored as no expression, 1%-49% scored as low expression, and >50% scored as high expression (Garon et al., 2015). A correlation between PD-L1 expression levels (>50%) and clinical benefit has been demonstrated in the KEYNOTE-010 study (Herbst et al., 2016). In fact, the FDA approval of pembrolizumab for NSCLC dictates that only tumors that test positive for PD-L1 using the companion assay can be treated with this inhibitor.

The PD-L1 28-8 pharm Dx (Dako) IHC assay is approved in patients with advanced NSCLC and melanoma receiving nivolumab with a scoring system defined as negative for a PD-L-1 expression of <1%, low expression that of 1%-5%, intermediate expression that of 5%-10% and high expression that of >10% (Borghaei et al., 2015). In contrast, the assay used for atezolizumab in advanced urothelial carcinoma or NSCLC (Ventana SP142 antibody assay) utilizes PD-L1 expression on both the tumor cells and the tumor-infiltrating immune cells with a final score of positivity combining both elements (Fehrenbacher et al., 2016). The fourth and last of the FDA approved assays is the one for durvalumab in advanced urothelial carcinoma, namely the Ventana SP263, where the PD-L1 expression is determined by the percentage of the tumor and the tumor infiltrating immune cells (Hahn et al., 2017; Massard et al., 2016).

In a recent study, these four FDA approved assays were evaluated by means of comparing the results of each assay on 39 NSCLC samples. It was shown that comparable percentage of PD-L1 stained tumor cells was only recorded in the 22C3, 28-8 and SP263 assays (Hirsch et al., 2017). In all four assays, the variability was greater in immune cell staining than in tumor cell staining and depending on the assay and the scoring system used, one third of the cases would have been classified differently. With regards to the tissue type to be used for the assay, both the fresh (HR 0.64; 95% CI: 0.50–0.83) and the archived tissue (HR 0.70; 95% CI: 0.54–0.89) provided the same results in the KEYNOTE-010 study; that is OS benefit was significantly higher with pembrolizumab compared to docetaxel.

It is therefore clear that although PD-L1 is the only biomarker currently recognized and used as predictive, it is by no means optimal and as our understanding of the TME increases the more evident it becomes that more markers are needed in order to accurately assess the clinical benefit from PD-1 or PD-L1 checkpoint blockade therapies.

A number of emerging predictive biomarkers are currently being considered as surrogate end points of response. Tumor mutation burden

(TMB) is defined as the total number of mutations per coding area in a tumor genome and this may range from a few to thousands of mutations. Increasing evidence shows that higher response rates to checkpoint inhibitors are associated with high tumor mutation burden in tumor types including melanoma (Snyder et al., 2014) and NSCLC (Carbone et al., 2017; Rizvi et al., 2015). In contrast, in tumors not responding to the PD1/PDL-1 axis inhibition (i.e. colorectal, ovarian and prostate cancer) the tumor mutation load is lower (Champiat, Ferte, Lebel-Binay, Eggermont, & Soria, 2014). Following FDA approval, in December 2017, the only test that is currently available which can detect TMB is a targeted sequencing panel known as Foundation One test (Foundation Medicine, Cambridge, MA, USA). This test has already been used in clinical trials to show that TMB can predict response to PD1-PDL-1 inhibitors in a variety of cancer types such as lung (Spigel et al., 2016) melanoma (Johnson et al., 2016) and urothelial cancer (Rosenberg et al., 2016). The recent approval of pembrolizumab for tumors with a particular genetic alteration (MSI-H) or (d-MMR) is based on evidence that tumors carrying DNA mismatch repair mutations exhibit response to PD1-PD-L1 inhibition and not surprisingly these tumors have a high mutation load (Le et al., 2017). Tests to measure d-MMP or MSI-H are already available through a different indication (genetic syndrome associated with familiar colorectal cancer) and can be used to assess TMB.

Although the role of immune TME (and its parameters) in predicting response to checkpoint inhibition is not fully understood yet, the presence of tumor-infiltrating lymphocytes (TILs) is shown to be associated with improved prognosis. For instance, immunoscore (Galon et al., 2006) is an example of an immune test that can measure the T cell infiltration – in FFPE– in colorectal carcinoma while it is currently being assessed in other tumor types as a predictive biomarker of checkpoint inhibition.

Potentially of value (but currently at an early stage of validation) are other predictive biomarkers to checkpoint inhibition therapy. The density of CD8+T-cells at the invasive margin of pre-treatment tumor samples has been shown to correlate with anti-PD1 (pembrolizumab) response. In a study by Tumeh et al. (2014) samples from patients with metastatic melanoma showed that tumor regression after therapeutic PD-1 blockade requires pre-existing CD8(+) T cells that are negatively regulated by PD-1/PD-L1-mediated adaptive immune resistance, providing the rationale for further exploration of these markers.

Regulatory T cells (Tregs) are considered negative regulatory cells resulting in peripheral immune suppression and their role as a predictive biomarker has been evaluated in melanoma patients in response to nivolumab (Woods, Ramakrishnan, Sodré, Berglund, & Weber, 2017). Tregs had a decreased suppressive function in responding patients ($p = 0.03$) but not in non-responders. In addition, increased phosphoSTAT3 (pSTAT3) expression in Tregs was detected in responding patients ($p = 0.01$) versus non responders leading to the suggestion that pSTAT3 induction and reduced suppressive function may serve as biomarkers of melanoma patient response to nivolumab.

4. Conclusions

With around 2000 immunotherapeutic agents currently in development, the cancer therapy landscape is changing rapidly. The addition of immunotherapy as a cancer treatment modality, over the last few years, has opened up new and exciting possibilities in the therapeutic management of cancer. The development of immune checkpoint inhibitors in particular PD-1 and PD-L1 inhibitors has introduced an exciting era in the management of different cancer types with some of these agents now considered the standard of care for malignancies such as melanoma and NSCLC (by offering durable responses irrespective of tumor's histological subtype or mutation status). Such agents have found wide applicability including some of them having already received regulatory approval for their use either alone or in combination.

At the same time, it is clear that not all patients derive clinical benefit from PD-1 or PD-L1 checkpoint blockade therapies, and a lot of issues remain to be solved including: i) long term outcomes, ii) associated toxicity, iii) resistance of the individual immunotherapy agents and/or their combinations with other modalities, iv) optimal clinical trial design to reach fast and definitive conclusions, and v) development and validation of predictive biomarkers to guide disease management. Efforts to further elucidate the underlying mechanisms of action of the checkpoint blockade inhibitors and to expand the immune targets for combinational therapy (thereby potentially enhancing clinical benefit) are currently ongoing. Given the impressive achievements, in the field of immunotherapy, of the last decay one can only expect the role of this relatively new cancer treatment modaliy to lead to better therapeutic outcomes in these patients.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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