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Invited Review

Understanding and overcoming the resistance of cancer to PD-1/PD-L1 blockade

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ABSTRACT

Greater understanding of tumour immunobiology has led to a new era of cancer treatment in which immuno-oncology (IO) therapies are used to boost anti-cancer immune responses. Prominent among these therapies are immune checkpoint inhibitors (ICIs), antibody-based drugs that can unleash the power of tumour-specific CD8 + T-cells. ICIs targeting the Programmed cell death protein 1 (PD-1) cell surface receptor or its ligand PD-L1 are particularly effective, with clinical studies reporting powerful and durable therapeutic impact against many cancer types, including melanoma and non-small cell lung cancer. ICIs have the potential to transform the landscape of cancer treatment, and their development was recognised by the award of the 2018 Nobel Prize in Physiology or Medicine to James Allison and Tasuku Honjo. However, the proportion of patients responding to anti-PD-1/PD-L1 monotherapy can be low. The next major challenge involves understanding and overcoming the innate and acquired resistance that prevents most patients from responding to PD-1/PD-L1 blockade. In this review, we outline the physiological function of PD-1 and its exploitation by developing tumours. We give an overview of current FDA-approved drugs targeting PD-1 or PD-L1 and summarise clinical progress so far. We then discuss key mechanisms thought to underpin resistance to PD-1/PD-L1 blockade, describing biomarkers that could allow patient responses to be predicted before treatment, and tracked once treatment has started. We also present clinical and pre-clinical combination therapies that have been developed to overcome resistance and which have the potential to substantially extend the therapeutic reach of these revolutionary drugs.

1. Introduction

Cancers arise through the accumulation of DNA mutations and epigenetic modifications that conspire to allow cells to overcome control mechanisms that regulate an array of cellular processes, including metabolism, proliferation, survival, and invasion [1]. It is now clear that the immune system has a complex role in tumour development. Certain immune cells and immunological mechanisms can aid tumour development by helping to create a supportive tumour microenvironment (TME) that contains blood vessels, lymphatic channels, and other stromal cells, as well as immune cells [2]. However, tumours also need to evolve the ability to evade or suppress any immune processes that compromise their growth and survival. The goal of immunotherapy is to overcome these evasion and suppression mechanisms, and enable immune cells, particularly CD8+ cytotoxic T cells, to mount an attack against the cancer. There have been major experimental and clinical achievements in this area in recent years, none more so than the development of antibody-based drugs that block signalling through PD-1. One of the many ways that tumours evolve to suppress immune attack is by exploiting the natural T-cell suppressive properties of this immune checkpoint protein, which is a cell surface receptor for two PD-1 ligands (PD-Ls) called PD-L1 and PD-L2. Antibodies targeting PD-1 or PD-L1 have had impressive and durable effects in a small subset of patients with certain types of cancer. This has been instrumental in fuelling the

Abbreviations: Ag, antigen; APC, antigen-presenting cell; CAR, chimeric antigen receptor; CDK, cyclin-dependent kinase; CTL, cytotoxic T-cell; DC, dendritic cell; DAMP, damage-associated molecular pattern; dMMR, defective mismatch repair; FDA, US Food and Drug Administration; GM-CSF, granulocyte-macrophage colony stimulating factor; HLA, Human Leukocyte Antigen; ICI, immune checkpoint inhibitor; IFN, interferon; IFNγ, interferon-gamma; IL, interleukin; IO, immuno-oncology; irAE, immune-related adverse event; MHC, major histocompatibility complex; MSI-H, microsatellite instability-high; NK, natural killer; NSCLC, non-small-cell lung carcinoma; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L, programmed death ligand; PFS, progression-free survival; SCCHN, squamous cell carcinoma of the head and neck; SLT, secondary lymphoid tissue; TCR, T-cell receptor; Th, T helper; TIL, tumour-infiltrating lymphocyte; TLR, Toll-like receptor; TME, tumour microenvironment; Treg, regulatory T-cell

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current excitement surrounding IO therapies, but many patients are resistant, or only respond transiently, to these drugs. Predicting and tracking responsiveness requires the identification of reliable biomarkers, while an in depth understanding of mechanisms of resistance is required to extend the reach of these new drugs and allow their incorporation into rational combination therapies. We explore all these concepts, advances and challenges in this review, but to put this in context we first provide an overview of immune evasion/suppression by cancers and summarise the physiological functions of the PD-1/PD-L axis in immune regulation.

2. Immune evasion and suppression by cancers

Anti-tumour immune responses drive a process called 'cancer immunoediting', which, in its simplest form, involves three phases referred to as the 3E's: Elimination, Equilibrium and Escape [3]. In the elimination phase, immune cells detect and destroy aberrant or stressed cells with tumorigenic potential. This provides protection from cancer and explains why systemic immunosuppression increases the risk of many different types of cancer, including those in which infection is not a contributing factor [4,5]. However, mutations may cause pre-cancerous cells to emerge that are inherently less susceptible to detection and destruction by immune cells, or that are capable of suppressing anti-tumour immune attack [6]. Consequently, the nascent tumour may enter an equilibrium phase in which immune cells destroy some aberrant cells, but others survive. The surviving cells accumulate additional mutations and epigenetic changes, some of which could further enhance immune evasion and/or local immunosuppression. This will ultimately give rise to an 'immunoedited' population of tumour cells that have escaped from anti-tumour immune responses to such an extent that, provided other mechanisms of cellular control have been subverted, a clinically-significant cancer can form, invade and metastasise [3].

How tumour cells acquire immune evasion and suppression mechanisms, and indeed other pro-tumour properties, can be seen as a Darwinian process driven by random mutation and the subsequent selection of cells with a survival advantage. As a consequence, each patient's cancer is unique, and there can be considerable tumour cell heterogeneity within a patient, particularly during metastasis when distinct tumour cell clones may evolve different survival mechanisms. A whole variety of processes have been defined that allow cancers to evade immune attack or suppress anti-tumour immune responses, and more than one mechanism may be at work in a single tumour or patient. These processes can be cell-autonomous, reducing the immune sensitivity of the tumour cell, or can be driven by tumour cell-mediated modulation of the TME. They often involve the exploitation of physiological mechanisms of immunosuppression. They may not fully subvert anti-tumour immune responses, but they are sufficient to allow a cancer to develop to a point that it becomes clinically relevant. IO therapies aim to interfere with the immune evasion and immunosuppression mechanisms that a cancer has evolved in the hope that the power of anti-tumour immune responses can be unleashed.

Many immune cell types have proven anti-cancer activity, including natural killer (NK) cells and certain types of macrophages. However, it is T-cells that lie at the heart of ICI therapy. T-cells are also the focus of chimeric antigen receptor (CAR)-based technologies [7] and tumour-infiltrating lymphocyte (TIL) infusion therapy [8,9], two other IO approaches where considerable clinical advances have been made over the last few years. Broadly speaking, there are three main types of T-cells: CD8+ cytotoxic T-cells (CTLs), regulatory T-cells (Tregs), and CD4 + T helper (Th) cells, the latter of which can differentiate into a variety of different forms (e.g. Th1, Th2, Th17). Activated CTLs can kill cells, including tumour cells; Tregs are immunosuppressive and can aid tumour formation by suppressing other immune cells; and activated Th cells produce cytokines that shape immune and inflammatory responses, and have pro- or anti-tumour activity depending on their cytokine profile and context. Cancers evolve ways of encouraging pro-tumorigenic T-cells and evading, or suppressing, T-cells that have anti-cancer properties. One way this can be achieved is by exploiting PD-1 and the PD-Ls, which, as explained in the next section, collectively represent a natural axis of T-cell suppression.

3. Physiological role of the PD-1/PD-L axis in T-cell biology

The balance between positive and negative regulation of T-cells is crucial to maintain immune tolerance, prevent autoimmunity and avoid excessive immune responses, whilst also providing protection from infection and mediating tissue repair. Under normal physiological conditions and during infection, the PD-1/PD-L axis is a vital negative regulator of T-cells [10].

In order for a naive T-cell to develop effector functions (e.g. cell killing, cytokine production) it must first become fully activated by receiving three stimulatory signals from dendritic cells (DCs). This occurs in secondary lymphoid tissues (SLTs), such as lymph nodes. The first signal comes through the T-cell receptor (TCR): each T-cell carries a unique TCR and will transmit signals into the T-cell when it recognises its specific peptide antigen (Ag) presented by DCs in the context of Major Histocompatibility Complex (MHC) (referred to as Human Leukocyte Antigen (HLA) in humans). MHC class I (MHCI) and MHC class II (MHCII) present Ags to CD8+ and CD4 + T-cells, respectively. The second signal is via costimulatory receptors: CD28 is particularly important and is activated to signal after engaging its ligands B7-1/2 (CD80/86) on DCs. The third signal is provided by cytokines, such as interleukin (IL)-12, that are produced by DCs or other immune cells. DCs are licensed by CD4+ T-cells to enable them to efficiently prime CD8+ T-cells. Importantly, T-cell activation is balanced by negative signals transmitted through other receptors that become expressed on the activated T-cell shortly after its activation, or when it has migrated from the SLT to the tissue where it will exert its functions. PD-1 is one of many such molecules, which are collectively referred to as immune checkpoints.

PD-1 (CD279) is a type I transmembrane cell surface receptor that is a member of the CD28 receptor family. Naïve T-cells do not express PD-1, but it is upregulated on T-cells following Ag stimulation and in response to cytokines induced by T-cell activation, such as IL-2, IL-7, IL-15 and IL-21 [11,12]. PD-1 can also be expressed by B-cells, monocytes and DCs [13], and regulate various aspects of their immune function [14,15], so although it's expression by T-cells is critical during ICI therapy, it is worth bearing in mind that ICIs targeting the PD-1 axis will be interfering with PD-1 signalling on other cells too.

The PD-1 ligands PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273) [16–18] are type 1 transmembrane glycoproteins that are members of the B7 ligand family. Both are upregulated by pro-inflammatory cytokines, particularly type 1 and type 2 interferons (IFNs) although other cytokines including IL-4, IL-10 and granulocyte-macrophage colony stimulating factor (GM-CSF) [19] can also enhance PD-L expression. PD-L1 can be expressed by activated T-cells and B-cells, as well as some non-haematopoietic cells [13,20], while PD-L2 is found primarily on myeloid cells, such as monocytes, macrophages and mast cells [13]. Both can be expressed on DCs and other Ag-presenting cells (APCs) where they are well placed to regulate T-cell function.

Engagement of PD-1 by PD-L transmits inhibitory signals that suppress T-cell function. This is driven in part by the dephosphorylation of CD28, which counteracts T-cell activation signals [21,22]. PD-1-induced signals can dampen T-cell-mediated effector responses in inflamed tissues by preventing production of IL-2 (a cytokine essential for T-cell survival and proliferation); limiting production of Bcl-xL, an anti-apoptotic protein; and decreasing activity of NF-κB, a transcription factor associated with T-cell effector functions [23,24]. Experimental disruption of the PD-1 pathway can lead to uncontrolled T-cell responses, autoimmunity, and the collapse of immune tolerance. Mice lacking PD-1 develop autoimmune lupus-like symptoms (e.g. arthritis

and glomerulonephritis) due to increased T-cell activation [25]. However, T-cell inhibition by the PD-1/PD-L axis can be reversed once signalling through PD-1 ceases. For example, to avoid tissue damage during persistent LCMV infection, the PD-1/PD-L1 axis suppresses LCMV-specific T-cells and makes them acquire what is referred to as an 'exhausted' phenotype, but blocking signalling through PD-1 with anti-PD-L1 antibodies rescues many of these exhausted LCMV-specific T-cells and allows them to exert their effector functions again [26]. Thus, physiologically the PD-1/PD-L axis is vital for suppressing T-cell responses so that autoimmunity and tissue damage are avoided.

4. Tumour exploitation of the PD-1/PD-L axis

Tumours are often highly immunogenic. Some, like cervical cancer, harbour Ags from viruses that were important aetiological agents in tumour development [27], and most will contain neo-antigens (neo-Ags) generated from proteins encoded by the many mutated genes present in the cancer [28] or from aberrant transcripts produced in the dysfunctional setting of the cancer cell nucleus [29]. Patrolling DCs will pick up proteins released from dead tumour cells, including foreign proteins and aberrant self-proteins, and tumour-specific Ags derived from these proteins will be presented on MHC to naïve T-cells in SLTs. This will generate tumour-specific effector Th cells and activated tumour-specific CTLs capable of killing tumour cells. The tumour can avoid the effector functions of anti-tumour T-cells by evolving ways of blocking their entry into the TME, or by preventing their activation in the first place by interfering with the presentation of tumour-derived Ags by DCs. However, in many cancers T-cells specific for tumour Ags are found in the TME. Indeed, high levels of CTLs in the TME is typically a good prognostic indicator [30,31], suggesting that, in certain areas of a tumour at least, T-cells may still be capable of directing their effector functions against tumour cells. However, the cancer would not exist if it had not evolved ways of preventing these T-cells from exerting their full anti-tumour activity. This can be done by, for example, evading the target cell detection mechanisms of T-cells or suppressing the effector functions of the anti-tumour T-cells. Indeed, effector T-cells in the TME often have an anergic or 'exhausted' phenotype. Because of its natural T-cell suppressive properties, signalling through PD-1 is an obvious way that tumours could hold T-cells in check: this can be achieved by up-regulating PD-L expression on tumour cells, or on stromal and immune cells in the TME (Fig. 1, left panel). Early mouse experiments proved that the PD-1/PD-L axis could suppress anti-tumour immune responses *in vivo*. For example, in immunocompetent mouse models of myeloma, tumours were found to upregulate surface PD-L1 to reduce T-cell effector functions [32], while the growth of transplanted tumour cells could be reduced by using PD-1-deficient, rather than wild-type, mice [33]. In humans, PD-L1 expression was found to be up-regulated in a subset of tumours from a variety of different solid cancer types, and often correlated with poor prognosis and reduced survival [19]. For example, Li and colleagues demonstrated that PD-L1 expression was associated with reduced overall survival in patients with breast cancer [34]. Likewise, in several cancer types the expression of PD-1 by tumour-infiltrating T-cells has been linked to poor outcome and the presence of exhausted T-cells [35–37]. Collectively, pre-clinical studies, combined with the observations in human cancers, paved the way for the development of therapeutic antibodies capable of blocking the PD-1/PD-L axis in humans.

5. PD-1 and PD-L1 as IO targets

Antibodies targeting PD-1 or PD-L1 were developed that were able to suppress the growth of established tumours in a variety of mouse models [32,38–41]. In experimental and clinical settings, the Ag-specificity, reactivation and/or de novo generation of tumour-specific CTLs has been the principal focus of research (Fig. 1, right panel), but effector Th cells also have key anti-tumour functions that could be exploited therapeutically and which might be involved in mediating responses to antibodies targeting PD-1 or PD-L1 [42]. They could also be affecting the non-T-cell PD-1-expressing cells discussed above and might even have direct effects on malignant cells. For example, interfering with PD-L1 signalling motifs can increase the sensitivity of tumour cells to IFN-mediated cytotoxicity [43], and anti-PD-L1 antibodies can have a negative impact on tumour cell metabolism by reducing expression of enzymes associated with glycolysis, suppressing glucose uptake, and reducing AKT phosphorylation [44]. In addition, PD-1 can be expressed by subsets of human melanoma cells and is capable of directly enhancing tumour growth in mice via PD-L1-dependent activation of the mTOR pathway [45].

The first two humanised antibodies developed targeting the PD-1/PD-L axis in humans were the anti-PD-1 antibodies pembrolizumab and nivolumab (Table 1). Clinical trial data showed the efficacy and safety of these drugs compared to certain standard treatments, first in melanoma and then in several other cancer types. Over the last five years, this has led to the US Food and Drug administration (FDA) approving pembrolizumab and nivolumab for the treatment of a range of cancers (Table 1). In some cases, remarkably durable responses have been observed in small numbers of patients, resulting in unprecedented periods of disease-free survival. The highest objective response rates (ORRs) to single agent PD-1/PD-L1 blockade have been seen in patients with Merkel cell carcinoma (56%) [46,47], desmoplastic melanoma (70%) [48], or relapsed or refractory Hodgkin's lymphoma (87%) [49], and in these diseases complete response rates vary from 15% to 32%.

The impact of anti-PD-1 antibodies on tumours has been explored by using whole-exome, transcriptome and intratumoural TCR sequencing to analyse advanced melanomas in responding patients before and after nivolumab therapy [50]. Nivolumab reduced mutation and neo-Ag load; increased the presence of certain immune cell subsets in the tumour; changed the intratumoural TCR repertoire with expansion of specific CD8 + T-cell clones; and activated specific transcriptional networks in the tumour cells [50]. These observations are consistent with nivolumab inducing the activation of tumour-specific T-cells which subsequently attack the tumour. Other immune checkpoint genes were also upregulated in the tumours of responding patients [50], indicating that other ways of suppressing T-cells may evolve in nivolumab-treated patients. Other studies have sought to more precisely characterise the T-cell populations that are activated by PD-1/PD-L1 blockade in responsive patients: these studies are discussed in more detail in Section 6.6.

In addition to pembrolizumab and nivolumab, anti-PD-1 antibody toripalimab has received conditional approval in China for treating unresectable or metastatic melanoma [51] and antibody-based drugs targeting PD-L1 have also been developed, namely atezolizumab, durvalumab and avelumab. After positive results in clinical trials, these drugs received FDA approval for the treatment of certain cancers (Table 2). There are so many ongoing clinical trials involving drugs targeting the PD-1/PD-L1 axis that it is likely that their use as monotherapies in other advanced cancers will receive FDA approval in the coming months and years. Their use in a variety of other clinical settings, or as part of combination therapies, will also no doubt expand too: this is discussed in more depth in Section 7. On a cautionary note, there are some concerns that PD-1/PD-L1 blockade may promote tumour growth in some patients, a phenomenon referred to as hyperprogression [52], with a recent study reporting that as many as 20% of patients with NSCLC treated with PD-1/PD-L1 inhibitors might enter a hyperprogressive state defined by increased tumour growth rate and rapid progression to treatment failure [53]. Further studies are required, but these findings clearly emphasise the need to identify patients (prior to, or shortly after, initiating treatment) that are likely to develop anti-tumour responses as a result of PD-1/PD-L1 blockade.

To highlight the impact of PD-1/PD-L1 blockade, we next summarise some of the key clinical data that demonstrate that, in some tumour types, these therapies can be more effective and safer than

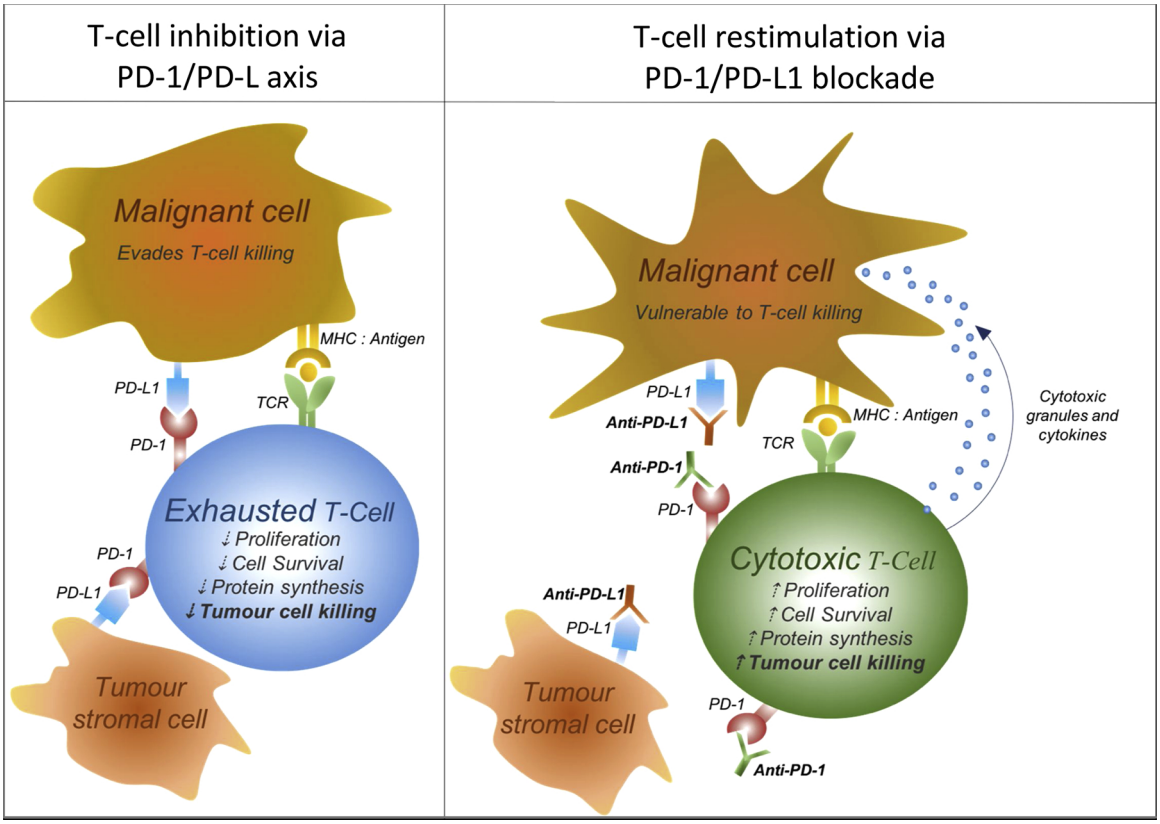

Fig. 1. T-cell inhibition in cancers can be mediated by the PD-1/PD-L axis and disrupted by PD-1/PD-L1 blockade therapy. **Left panel:** PD-L on malignant, stromal and/or immune cells within the TME can engage PD-1 expressed on infiltrating T-cells. This induces a cascade of inhibitory signals in the T-cell that can overcome activation signals and results in a T-cell with an 'exhausted' phenotype. **Right panel:** Treatment with anti-PD-1/anti-PD-L1 antibodies impedes PD-1 and PD-L engagement, preventing T-cell exhaustion, and allowing the T-cell to mediate cancer cell killing.

chemotherapy or other IO therapies.

5.1. PD-1/PD-L1 blockade compared to chemotherapy

In certain cancers, clinical data have demonstrated the improved efficacy and safety of PD-1/PD-L1 blockade compared to standard chemotherapeutics. For example, in a phase III trial involving patients with untreated melanoma lacking the BRAF mutation, responses to nivolumab were compared to those achievable with dacarbazine [54], the only FDA-approved chemotherapeutic for metastatic melanoma [55]. 210 patients received nivolumab every 2 weeks; 208 patients received dacarbazine every 3 weeks [54]. The ORR to nivolumab was 40% compared with 13.9% in dacarbazine-treated group, while the one-year survival rate was 72.9% and 42.1%, respectively. Moreover, only 11.7% of patients receiving nivolumab experienced grade 3/4 adverse events (i.e. severe/life-threatening or disabling) compared with 17.6% of those on dacarbazine.

Similar results were seen in a phase III trial of atezolizumab in patients with previously-treated squamous or non-squamous non-small cell lung carcinoma (NSCLC) [56]. 425 patients received atezolizumab; 425 received the chemotherapeutic docetaxel. Patients with tumours categorised as PD-L1+ (i.e. ≥ 1% of tumour cells expressing PD-L1) had a median overall survival of 15.7 months when treated with atezolizumab compared with 10.3 months with docetaxel. Interestingly, patients with lower or undetectable levels of intratumoural PD-L1 also had improved median overall survival rates on atezolizumab (12.6 months) compared to docetaxel (8.9 months). Additionally, grade 3/4 adverse events were less frequent in the atezolizumab group (15% compared to 43%). Two phase III trials have compared pembrolizumab to platinum-based chemotherapy in patients with previously untreated PD-L1-expressing advanced NSCLC [57,58]. In the first study [58], 305 patients with 50% or more PD-L1+ tumour cells were included, while the more recent study [57] evaluated 1274 patients whose tumours lacked *EGFR* mutation or *ALK* translocation and had > 1% PD-L1+ tumour cells. In both cases, pembrolizumab gave longer progression-free and/or overall survival with fewer adverse events, with the magnitude of overall survival benefit increasing with increased percentage of tumour cells expressing PD-L1.

These trials highlighted that PD-1/PD-L1 blockade had greater efficacy and a better safety profile than chemotherapies in patients with melanoma or NSCLC. It is also notable that patient-reported health-related quality of life has been found to be greater in NSCLC patients treated with pembrolizumab compared to those receiving docataxel [59].

5.2. PD-1/PD-L1 blockade versus ipilimumab

PD-1 blockers were not the first ICIs to enter the clinic. Ipilimumab takes this honour, a humanised antibody that binds the immune checkpoint protein CTLA-4. CTLA-4 inhibits T-cells during their initial activation [60–62], so ipilimumab was designed to enhance the generation of anti-tumour effector T-cells, and it is clear from human and murine studies that anti-CTLA-4 and anti-PD-1 antibodies target different populations of effector T-cells [63]. Ipilimumab also appears to affect Tregs. Tregs express more CTLA-4 than other T-cells and it is likely that ipilimumab works, at least in part, by inducing myeloid cell-mediated, Fc receptor-dependent, antibody-dependent cytotoxicity of CTLA-4-expressing Tregs to eliminate Treg-mediated suppression of the anti-tumour response [64–68]. Some patients with melanoma show strong and durable responses to ipilimumab, and in 2011 it was licensed in the EU and the US for the treatment of patients with unresectable or metastatic melanoma. However, it had significant toxicity

Table 1
PD-1 blockers approved for clinical use as monotherapies by the FDA.

Agent *Other Names* (Manufacturer)	Description	FDA-Approved Clinical Use (Year of Approval)
Nivolumab *Opdivo* *MDX1106b* *BM936558* (Bristol-Myers Squibb)	Human IgG4 PD-1 antibody with a S228 P hinge region mutation to reduce IgG4 Fc exchange.	**Unresectable or metastatic melanoma** with disease progression following ipilimumab treatment or positive for BRAF V600 mutation and progression following BRAF inhibitor treatment (2014). **Advanced renal cell carcinoma** following anti-angiogenic therapy (2015). **Metastatic squamous and non-squamous NSCLC** with disease progression during or after platinum-based chemotherapy (2015). **Unresectable or metastatic BRAF V600 wild-type melanoma** in combination with ipilimumab (2015). **Recurrent or metastatic SCCHN** with disease progression during or after platinum-based chemotherapy (2016). **Classical Hodgkin lymphoma** that has progressed after autologous HSC transplantation and post-transplantation brentuximab vedotin (antibody-drug conjugate) treatment (2016). **Urothelial carcinoma** locally advanced or metastatic disease that progressed during or following platinum-based chemotherapy or within a year of neoadjuvant/adjuvant treatment (2017). **Hepatocellular Carcinoma** in patients intolerant to, or showed progression after, treatment with chemotherapeutic, Sorafenib (2017). **Metastatic colorectal cancer** with progression following fluoropyrimidine, oxaliplatin, irinotecan treatment and ≥12 years old with dMMR and MSI-H disease (2017). **Melanoma with involvement of lymph nodes or metastatic disease** following complete resection (2017). **Metastatic SCLC** progressing after platinum-based chemotherapy and any other therapy (2018).
Pembrolizumab *KEYTRUDA* *Lambrolizumab* *MK3475* (Merck)	Humanised IgG4κ PD-1 antibody with a C228 P mutation to prevent cytoxicity caused by Fc interaction.	**Unresectable or metastatic melanoma** with disease progression following Ipilimumab treatment or positive for BRAF V600 mutation and progression following BRAF inhibitor treatment (2014). **Recurrent or metastatic PD-L1 + NSCLC** with disease progression during or after platinum-containing chemotherapy (2016). **Metastatic SCCHN** with progression during or after platinum-containing chemotherapy (2016). **Adult and pediatric Hodgkin lymphoma** that is refractory, classical or has relapsed after ≥3 rounds of treatment (2017). **Locally advanced or metastatic urothelial carcinoma** in patients not eligible for cisplatin-containing chemotherapy or with disease progression during/after platinum-containing chemotherapy (2017). Updated in 2018 to require use of an approved diagnostic test to assess PD-L1 levels in tumour of those not eligible for cisplatin-containing chemotherapy. **Locally advanced or metastatic gastric or gastroesophageal junction PD-L1 + adenocarcinoma** with disease progression after two or more systemic therapies (including fluoropyrimidine- and platinum-containing chemotherapy) (2017). **Adult and pediatric unresectable or metastatic MSI-H or dMMR solid tumours** that progressed following treatment and have no alternative treatment options (2017). Tissue/site agnostic. **Unresectable or metastatic MSI-H or dMMR colorectal cancer** that has progressed following treatment with chemotherapeutics: fluoropyrimidine, oxaliplatin and irinotecan (2017). **Recurrent locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma** positive for PD-L1 expression assessed by an approved diagnostic test (2018). **Adult and pediatric refractory PMBCL** that has relapsed after ≥2 other therapies (2018). **Hepatocellular carcinoma** previously treated with sorafenib (2018). **Merkel cell carcinoma** adult or pediatric, recurrent, locally advanced or metastatic (2018). **Recurrent or metastatic cervical cancer** with disease progression on or after chemotherapy when tumours express PD-L1 (≥1%) as determined by an FDA-approved test (2018). **Melanoma with involvement of lymph node(s)** adjuvant after complete resection (2019). **Stage III PD-L1 + NSCLC** who are not candidates for surgical resection or definitive chemoradiation (2019).

Abbreviations: HSC, haematopoietic stem cell; dMMR, defective mismatch repair; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; PMBCL, primary mediastinal B-cell lymphoma; SCCHN, squamous cell carcinoma of the head and neck; SCLC, small cell lung cancer. Prepared using data from FDA.gov.

in many patients, including those that showed no anti-tumour response: these were probably on-target toxicities resulting from profound effects on Tregs and effector T-cells.

A phase III trial directly compared the efficacy and toxicity of ipilimumab with pembrolizumab in patients with advanced melanoma [69]. 834 patients received either 10 mg/kg pembrolizumab every two or three weeks, or 3 mg/kg ipilimumab every three weeks. Reports of grade 3–5 treatment-related adverse events (severe/life-threatening or disabling/death) were lower in the pembrolizumab-treated group (10.1–13.3%) than the group that received ipilimumab (19.9%). Efficacy was also greater with pembrolizumab resulting in an ORR of 33% compared with 11.9% in ipilimumab-treated patients. 6-month

Table 2
PD-L1 blockers approved for clinical use by the FDA.

Agent *Other Names* (Manufacturer)	Description	FDA-Approved Clinical Use (Year of Approval)
Atezolizumab *Tecentriq* *MPDL328DA* (Roche)	Phage-derived human IgG1 PD-L1 antibody with mutation at 298 (N298A) to prevent binding to Fcγ receptors and inhibit ADCC and CDC.	**Metastatic NSCLC** with disease progression during or after platinum-containing chemotherapy (2016). **Advanced or metastatic urothelial carcinoma** in patients not eligible for cisplatin-containing chemotherapy or with disease progression during/after platinum-containing chemotherapy (2017). Updated in 2018 to require use of an approved diagnostic test to assess PD-L1 levels in tumour of those not eligible for chemotherapy containing cisplatin. **Breast cancer** PD-L1 + and unresectable, locally advanced or metastatic (2019).
Durvalumab *Imfinzi* *MEDI4736* (MedImmune)	Human IgG1κ PD-L1 antibody with triple mutation in heavy chain Fc region to inhibit ADCC and CDC.	**Locally advanced or metastatic urothelial carcinoma** with disease progression during or following platinum-containing chemotherapy or within a year of neoadjuvant or adjuvant treatment (2016). **Unresectable stage III NSCLC** with disease progression following concurrent platinum-based chemotherapy and radiotherapy (2018).
Avelumab *BAVENCIO* *MSB0010718C* (Merck and Pfizer)	Human IgG1 PD-L1 antibody with intact Fc region with potential to induce ADCC and CDC.	**Metastatic Merkel cell carcinoma** in patients ≥12 years old (2016). **Locally advanced or metastatic urothelial carcinoma** with disease progression during or following platinum-containing chemotherapy or within a year of neoadjuvant or adjuvant treatment (2016).

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; NSCLC, non-small cell lung cancer. Prepared using data from FDA.gov.

progression-free survival (PFS) was also better with pembrolizumab (47%) than ipilimumab (26.5%).

Thus, at least in the context of melanoma, PD-1/PD-L1 blockade appears to be a safer and more effective therapeutic than ipilimumab.

5.3. Side effects of PD-1/PD-L1 blockade

In addition to potentially inducing tumour hyperprogression [52,53], IO therapies are likely to cause collateral damage as a consequence of inducing an imbalance in the immune system. A potential risk with PD-1/PD-L1 blockade is on-target toxicities because the antibodies will inhibit PD-1 on all cells that express it, not just tumour-specific T-cells. This can result in immune-related adverse events (irAEs) due to enhanced T-cell responsiveness, increased T-cell effector functions, and the activation of self-reactive T-cells. This can be seen from common side effects of PD-1/PD-L1 blockade, which include fatigue, pruritus (severe itching of the skin), vitiligo (loss of skin pigment), diarrhoea and colitis (inflammation of the colon) [70]. Cases of tuberculosis have also been reported [71] and life-threatening pneumonitis can emerge as a late onset side effect of PD-1/PD-L1 blockade [72]. In trials involving patients with NSCLC, the incidence of pneumonitis ranged from 1 to 9% [73–77] and led to three treatment-related deaths in a phase I trial with nivolumab [73].

A recent systematic review of 35 randomized trials involving ICIs concluded that 14% of patients treated with PD-1/PD-L1 inhibitors suffered adverse events that scored ≥3, in contrast to 34% of patients undergoing CTLA-4 blockade, increasing to 55% during ICI combination therapy [78]. Toxicities associated with PD-1/PD-L1 blockade are also not as frequent, and often not as severe, as those resulting from chemotherapeutic agents or other IO therapies [56,69,79], and the majority of the irAEs it causes can be effectively treated with immunosuppressive drugs [70]. Such drugs might be expected to counteract the action of PD-1/PD-L1 blockade: however, a systematic review of 27 trials involving patients receiving corticosteroids and ICIs (including CTLA-4 and PD-1/PD-L1 inhibitors) reported no obvious therapeutic disadvantage to patients treated with ICIs when corticosteroids were used to alleviate the symptoms of irAEs [80]. Similarly, Weber and colleagues analysed data from four clinical studies involving treatment of patients with advanced melanoma with nivolumab [54,73,81–83] and found no significant differences in the ORRs of patients receiving immune-modulation alongside nivolumab compared to those patients receiving nivolumab alone [84]. Interestingly, the team also reported that patients who experienced irAEs had significantly higher ORRs but not PFS [84]. This suggests that a strong immune response following PD-1/PD-L1 blockade that is capable of inducing irAEs, may actually be beneficial in the initial regression of the tumour and that the irAEs can be mitigated without impacting the anti-tumour benefits of the ICI. However, the fact that PFS was not increased in the patients with irAEs, despite increased ORR, reiterates that initial response to PD-1/PD-L1 therapy does not always correlate with prolonged responses and highlights the issue of acquired resistance to treatment. Almost all IO clinical trials have excluded patients with pre-existing autoimmune disease to avoid a potential exacerbation of their condition, but a recent study examined 52 patients with advanced melanoma who had pre-existing autoimmune conditions (including rheumatologic, gastrointestinal, endocrine, dermatological and other autoimmune conditions) and were treated with anti-PD-1 antibody (pembrolizumab or nivolumab) [85]. 38% of patients experienced an exacerbation of their autoimmune condition, but most were successfully treated with immunosuppressive drugs. There were no treatment-related deaths, and only one patient discontinued anti-PD-1 antibody treatment due to the increased severity of their autoimmune symptoms. Moreover, with respect to their melanoma, these patients had an ORR of 33%, which compares favourably to the ORRs of 33–45% seen previously in anti-PD-1-treated patients that did not have a pre-existing autoimmune condition.

Thus, PD-1/PD-L1 blockade therapies result in fewer adverse events than many standard cancer treatments. These would be worth avoiding if a patient's cancer does not respond to PD-1/PD-L1 blockade, but adverse events that do occur, even in patients with pre-existing autoimmune conditions, can often be treated with immunosuppressive drugs without appearing to limit anti-cancer efficacy. Thus, the potential anti-cancer benefits of PD-1/PD-L1 blockade largely outweigh the risks of on-target and off-target toxicities. Moreover, it may be possible to alleviate side effects by modifying the anti-PD-1/PD-L1 antibodies. For example, Ishihara and colleagues have recently shown that the safety of anti-PD-L1 antibody in mouse models can be improved by fusing it to the collagen-binding domain of von Willebrand factor, thereby allowing it to bind to the tumour stroma and exert its effects locally [86]. Interestingly, this approach also enhanced treatment efficacy. Optimisation of dosing regimens could also reduce side effects. Indeed, in patients with previously untreated advanced

melanoma 3 mg/kg nivolumab plus 1 mg/kg ipilimumab resulted in a lower incidence of treatment-related adverse events than the currently approved 1 mg/kg nivolumab plus 3 mg/kg ipilimumab regimen, with no apparent change in efficacy [87].

Despite the clinical benefits of PD-1/PD-L1 blockade, most patients do not respond or do not show long-lasting remission after treatment. For example, in a Phase III trial involving 316 patients with advanced melanoma, 52 patients showed a complete response to treatment with nivolumab with a further 88 showing a partial response [88]. In a Phase III trial in patients with advanced NSCLC, only 1 of the 135 patients receiving nivolumab achieved a complete response, and just 26 showed a partial response [77]. This raises three key questions: Why are so many patients resistant to, or only respond transiently to, PD-1/PD-L1 blockade? Can a patient's response be predicted prior to treatment? Can targeting the PD-1/PD-L axis synergise with other treatments to create effective combination therapies?

6. Identifying responders and mechanisms of resistance

Patients that do not respond to PD-1/PD-L1 blockade are said to have 'innate resistance', while those responding transiently before their disease progresses have 'acquired resistance'. There is a need to develop accurate ways of predicting which patients will benefit from anti-PD-1/PD-L1 therapy, and if the mechanisms underpinning innate and acquired resistance can be understood, then it might prove possible to extend the use and clinical impact of PD-1/PD-L1 blockade by incorporating it into well-designed combination therapies.

For PD-1/PD-L1 blockade to work effectively, it is expected that a number of criteria must be met. This means that there are also multiple mechanisms tumours can exploit to become resistant to the therapy. First, the tumour must be sufficiently immunogenic to have the potential to fully activate T-cells specific for tumour Ags: weakly immunogenic tumours will have innate resistance if they cannot generate an activated population of tumour-specific T-cells to respond to PD-1/PD-L1 blockade. Second, the T-cells must be efficiently activated by these Ags, and successfully home to, and infiltrate, the TME: potentially immunogenic tumours will be resistant to PD-1/PD-L1 blockade if they have, or acquire after treatment, the ability to prevent the activation and/or infiltration of tumour-specific T-cells. Third, the PD-1 axis must play at least some role in suppressing pre-treatment, or therapy-induced, tumour-specific T-cells: PD-1/PD-L1 blockade will not be effective in patients in which the PD-1/PD-L axis is not being used to suppress T-cells. Fourth, tumour cells in the patient must not have, and must not evolve, effective PD-1-independent ways of evading or suppressing anti-tumour immune responses: such mechanisms will render PD-1/PD-L1 blockade partially or completely ineffective. Fifth, in response to PD-1/PD-L1 blockade, exhausted or anergic tumour-specific T-cells must proliferate and/or become activated and be sufficiently powerful to launch a clinically significant attack on the tumour: patients will be resistance to treatment if PD-1/PD-L1 blockade results in a qualitatively or quantitatively insufficient reinvigoration of exhausted tumour-specific CD8 + T-cells. Sixth, anti-tumour T cells that become activated by PD-1/PD-L1 blockade should ideally target tumour Ags derived from proteins essential for tumour growth, or collectively display specificity for a wide variety of tumour Ags, and these Ags must be displayed on MHC on the surface or tumour cells: tumours will be able to develop resistance through the evolution of tumour cell variants that have lost target Ags or the ability to present them. And seventh, for long-term remission, it is probable that a population of long-lived effector T-cells and/or memory T-cells needs to be generated: patients might initially respond to PD-1/PD-L1 blockade but are likely to relapse if the enlivened anti-tumour T-cells are short-lived. Clearly there is plenty of scope for patients to exhibit innate or acquired resistance to blockade of the PD-1/PD-L1 axis. Here we explore some of the mechanisms that may be responsible for this resistance: they are represented diagrammatically in Fig. 2.

6.1. Mutational burden

Between patients with a specific cancer type, there is extensive variation in tumour mutational burden [89]. In many cancers, high mutational burden (which can be measured in tumour biopsies or blood-borne tumour cells/DNA) is associated with a variety of positive outcomes for patients treated with PD-1 blockers, such as high ORR, extended PFS and/or durable benefit [90–97]. This is presumably because they contain more potential neo-Ags, increasing the chance of anti-tumour T-cells becoming activated and attacking the tumour. Some responsive cancer types are linked to long-term exposure to mutagens, such as melanoma (caused by exposure to UV light) and NSCLC (usually driven by DNA damaging agents in tobacco smoke) [98,99]. Tumours with defective mismatch repair (dMMR) have an increased DNA mutation rate, and these tumours also respond well: across 12 different cancer types, 21% of patients with dMMR-deficient tumours had complete responses to anti-PD-1 therapy, and 53% showed objective radiographic responses [100]. Interestingly, these types of clinical data led, in 2017, to pembrolizumab being the first FDA-approved 'tissue/site agnostic' drug in that it can now be used in patients with unresectable or metastatic tumours irrespective of their location, provided that they have dMMR or high microsatellite instability (MSI-H): patients also need to have progressed following previous treatment and have no other satisfactory treatment options [101]. Interestingly, C-to-A transversions are reported to be more common in patients who experience durable clinical benefit [91]. These patients had higher PFS, and an ORR of 53% compared with 17% for those with fewer transversion mutations. Specific gene deletions, absent from non-responders, were also found in patients who responded well to treatment [91]. Others have reported that responsive melanomas are enriched for mutations in the DNA repair gene *BRCA2* [90], while responsive glioblastomas are enriched for alterations in the MAP kinase signalling pathway and often lack *PTEN* mutations [102]. It is not clear how these mutations affect responsiveness to PD-1 blockers, but their absence could help identify patients prior to treatment that are likely to be resistant to the drugs.

Although some patients with tumours with a relatively low mutational burden have been seen to respond to PD-1/PD-L1 blockade [91], high mutational burden, dMMR and MSI-H are strong predictors of response. Conversely, low mutational burden, microsatellite stability and effective DNA repair mechanisms are usually associated with innate resistance to these drugs.

6.2. T-cell priming and infiltration of the TME

Tumours are highly heterogeneous and vary extensively with respect to effector T-cell infiltration. Those containing abundant T-cells are regarded as 'immunologically hot', while those with less T-cell infiltration are 'immunologically cold' [103–105] (Fig. 3). Tumours with extensive effector T-cell infiltrates, and cytolytic or interferon-γ (IFN-γ)-related gene expression profiles, typically respond best to PD-1/PD-L1 blockade [30,31,94,106–110]. Interestingly, across 22 tumour types, high mutational burden and a T-cell-inflamed gene expression profile were independently predictive of response to pembrolizumab [94].

The presence of effector T-cells in the TME is linked to mutational and neo-Ag burden, but responses to PD-1/PD-L1 blockade will also depend on the number and diversity of previously-activated tumour-specific T-cells present in the patient. Durable responses would be expected in patients with a population of anti-tumour T-cells capable of targeting numerous neo-Ags. T-cells are also likely to be beneficial if they are specific for neo-Ags derived from mutated proteins critical for tumour survival. In this respect, it is interesting that TILs capable of recognising neo-Ags arising from mutations common in the p53 tumour suppressor gene have been found in 8% of patients with epithelial tumours (n = 140) [111]. Also, memory T-cells specific for important mutated oncogenes are detectable in patients with tumours containing

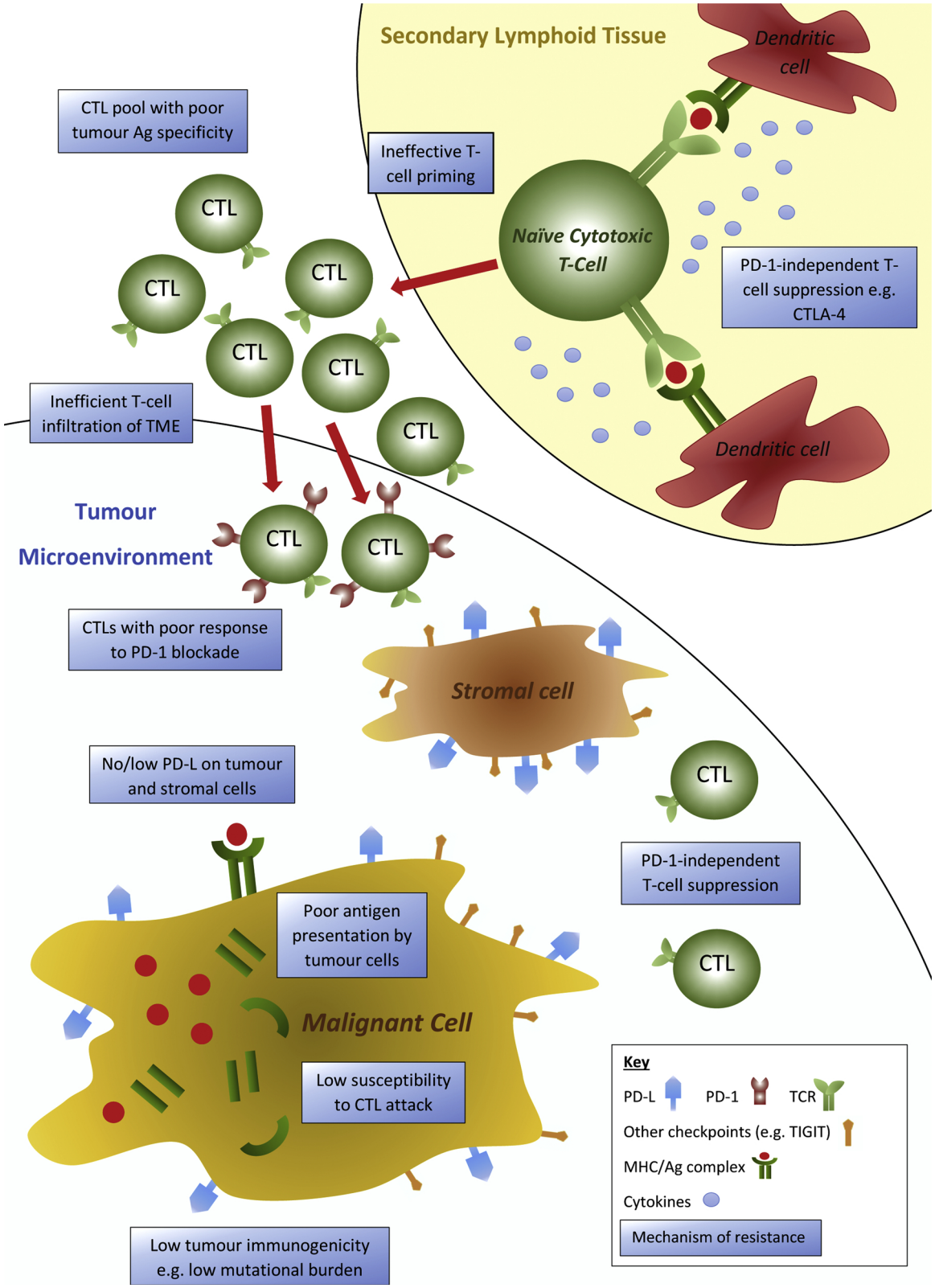

Fig. 2. Mechanisms of resistance to PD-1/PD-L1 blockade therapy. The figure shows the priming of anti-tumour cytotoxic T-cells (CTLs) by dendritic cells in secondary lymphoid tissues (yellow shape, top right) and the homing of the effector CTLs into the TME (light blue shape, left/bottom) which contains malignant cells and stromal cells. The blue boxes indicate specific characteristics that might be responsible for, or contribute to, innate and/or adaptive resistance to antibodies targeting the PD-1/PD-L1 axis. The symbols in the figure are defined in the key (bottom right). The green and red shapes in the malignant cell represent unformed MHC/Ag complexes.

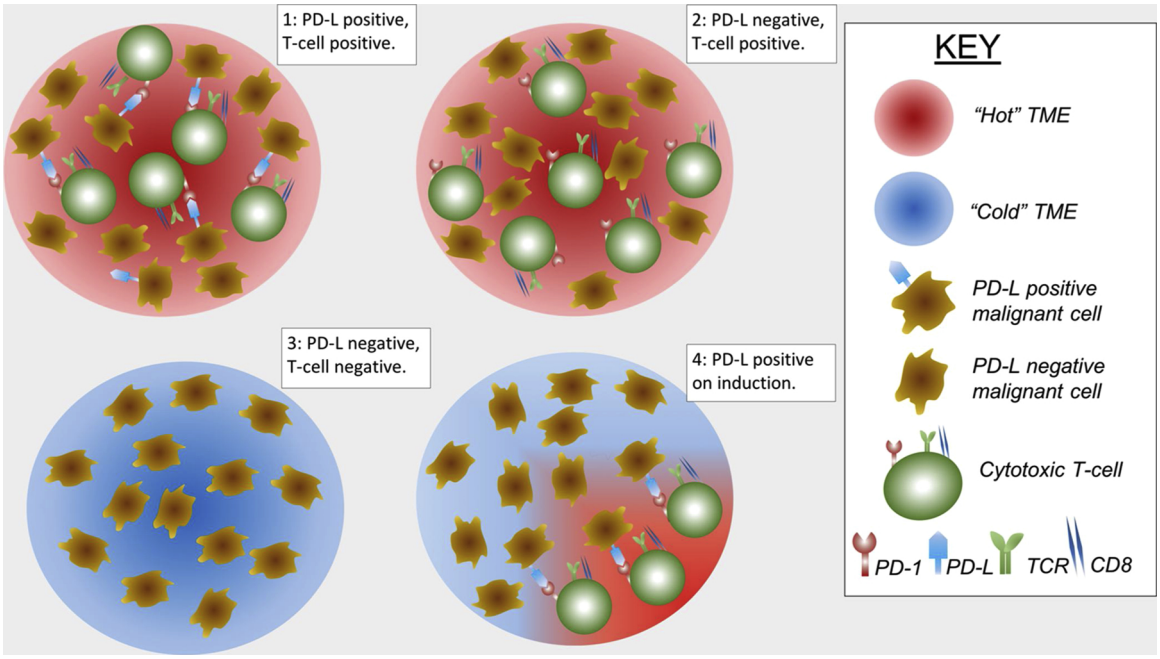

Fig. 3. Tumour variation in PD-L expression and T-cell infiltration. Tumour biopsies can be analysed by immunohistochemistry and classified as: (1) PD-L positive, T-cell positive; (2) PD-L negative, T-cell positive; or (3) PD-L negative, T-cell negative. (4) PD-L expression can be induced by inflammation. Tumours with a high level of immune cell infiltration are regarded at immunologically "Hot" and those with a low level as immunologically "Cold". It is important to note that biopsy samples may not always be representative of the tumour as a whole, or of metastases, so classifications based on a single biopsy may not accurately reflect tumour diversity in a patient.

these mutations [112] and in two patients that showed durable clinical benefit from PD-1/PD-L1 blockade monotherapy [113]. Interestingly, these two patients had not been expected to respond; one had PD-L1-negative NSCLC with low mutational burden, while the other had mismatch repair proficient colorectal cancer. The oncogene-specific T-cells, which were maintained for years after treatment initiation, may have been critically important in enabling the response [113].

Specific subsets of DCs prime naïve anti-tumour CD8 + T-cells and re-stimulate T-cells in the TME [114–117] so any disturbance in DC function [118] could interfere with anti-tumour T-cell responses. Migration is a key feature of DC biology and this, as with other leukocytes, is largely controlled by secreted proteins called chemokines [119]. Spranger and colleagues reported that, in mice, a reduction in the chemokine CCL4 was associated with reduced DC migration within the TME and to draining lymph nodes, and a reduction in tumour-specific T-cell infiltration of the TME [120]. Tumour DCs may do more than present tumour Ags: in a mouse model of melanoma, they produce the chemokines required to recruit effector T-cells [121], while IFN-γ-induced IL-12 production by intratumoural DCs is required for anti-PD-1 antibodies to successfully activate T-cells that eliminate subcutaneous tumours generated using mouse MC38 colon adenocarcinoma cells [122]. It is also notable that human breast and pancreatic cancers are reported to induce a systemic, G-CSF-dependent reduction in cDC1 DCs and their precursors: cDC1 are specialised activators of CD8 + T cells [123]. Moreover, low numbers of BDCA-3+ DCs in melanomas have been reported to correlate with poor responses to PD-1/PD-L1 blockade in humans [124], while in patients whose melanoma contains few Tregs, intratumoural density of cDC2 positively correlates with responsiveness to anti-PD-1 blockade [125]. cDC2 present Ag to CD4+ T-cells and, in mice, these T-cells can drive anti-tumour immune responses if Tregs are experimentally depleted [125].

Even if tumour-specific effector T-cells are generated, they need to enter the TME. Clearly there will be a growth advantage to the tumour if it evolves the ability to prevent this infiltration [126]. Epigenetic silencing, posttranslational modification and truncation of chemokines can reduce effector T-cell infiltration of the TME [127–129]. Stromal cells surrounding tumours can evolve the ability to prevent effector T-cell entry, and the TGF-β pathway appears to play a major role in inducing T-cell exclusion properties in peritumoural fibroblasts [130,131]. Moreover, a transcriptional programme in human melanoma has recently been defined that is associated with T-cell exclusion: it also predicted poor clinical responses to anti-PD-1 therapy, but could be suppressed by inhibitors of cyclin-dependent kinase (CDK) 4/6 [132].

In summary, tumours will be resistance to PD-1/PD-L1 blockade if there are insufficient numbers of tumour-specific effector T-cells in the patient, or if these cells are unable to enter the TME to execute their anti-tumour activities.

6.3. Expression of PD-1 ligands

A key requirement for responsiveness to PD-1/PD-L1 blockade is that tumour-specific T-cells in the patient are being inhibited through PD-1 before or during therapy. Tumour expression of PD-L1 and/or PD-L2 will suppress PD-1 + T-cells at the site where anti-tumour activity is required, but PD-1-mediated T-cell suppression elsewhere in the patient might also limit anti-tumour responses, and recent work in mice has revealed that PD-L1 + exosomes released from tumours can suppress T-cell activation in the tumour-draining lymph node [133]. PD-L1 can be expressed by immune cells and stromal cells in the TME, as well as by the tumour cells themselves, and these non-tumour cells are likely key sources of PD-1-mediated immunosuppression in many cancers [108,134–136]. A common way of attempting to predict resistance/responsiveness to PD-1/PD-L1 blockade, and which influences clinical decision-making, relies on analysing PD-L1 expression in tumour biopsies by immunohistochemistry [137]. PD-L1-positive, immunologically 'hot' tumours would be predicted to respond well to PD-1/PD-L1 blockade (Fig. 3). Indeed, intratumoural PD-L1 expression can correlate with responsiveness to PD-1/PD-L1 blockade [138] independently of tumour mutational burden [139], and the FDA requires approved diagnostic tests to be used to quantify PD-L1 in advanced or metastatic urothelial tumours to determine if pembrolizumab or

atezolizumab can be administered (www.fda.gov/Drugs/DrugSafety/ucm608075). However, at present, there is no universal system of classifying patients as PD-L1-positive or -negative and variation between studies regarding the proportion of cells that need to be expressing PD-L1 for a tumour to be designated as 'PD-L1-positive' [140]. Moreover, PD-L1 expression alone is not reliable at predicting responses to PD-1/PD-L1 blockade: in many cases, tumours classified as PD-L1-negative respond to treatment, and vice versa [113,137]. The classification techniques might be inaccurate: tumours are complex masses of multiple different cell types and the sampled area may not be representative of the whole tumour. Primary tumours and metastases differ considerably as well, so a biopsy of one tumour deposit might not accurately reflect those found elsewhere in the patient. In addition, tumours genuinely PD-L1-negative could be positive for PD-L2, so the patient could potentially respond to PD-1 blockade.

Many competing transcriptional and post-transcriptional mechanisms regulate PD-L1 expression [141]. Expression on tumour cells can be the result of the inflammatory and hypoxic environment of the TME, and Toll-like receptor (TLR) ligands and a variety of cytokines can increase PD-L1 expression on many cells types. Recruitment of activated T-cells into the TME can increase production of inflammatory mediators which, in turn, can induce expression of PD-L1 on tumour cells, particularly at the invasive margin where T-cells are often in abundance (Fig. 3) [142,143]. Translational and post-translational regulation is also important. Over-expression of the Myc oncogene collaborates with mutated K-Ras to enhance translation of PD-L1 mRNA [144], while type-3 transmembrane proteins CMTM4 and CMTM6 exert post-translational regulation to control cell surface expression of PD-L1 in tumour cells and DCs [145,146]. In addition, N-glycosylation stabilises PD-L1 and is essential for its interaction with PD-1: antibodies that target glycosylated PD-L1 induce its internalisation and degradation, and, when they are coupled to an anti-mitotic drug, can kill PD-L1 + tumour cells, and bystander PD-L1-negative tumour cells, in mice [147]. It has also been recently reported that PD-L1 is stabilised by palmitoylation: preventing this lipid modification in MC38 tumour cells increases *in vivo* anti-tumour immunity against these cells in mice [148]. The extent of production and release of soluble forms of PD-L1 might contribute to resistance to PD-L1 blockade therapy. Such variants, which lack the transmembrane domain as a result of alternative splicing, have been found in NSCLC patients that relapsed after anti-PD-L1 antibody treatment and are able to act as soluble decoys for anti-PD-L1 antibodies [149].

Tumour mutational burden and PD-L1 expression are not significantly correlated within most cancer types [139], but the mutational landscape of the tumour can influence PD-L1 expression [141,150]. Translocations or amplifications of the locus containing the closely linked *PD-L1* and *PD-L2* genes are found in subsets of certain tumours, including Hodgkin's lymphoma and NSCLC [141]. Loss of PTEN can cause constitutive expression of PD-L1 by activating the Akt pathway [151,152]. PD-L1 expression can also be induced by mutations that activate EGFR or K-Ras [153,154] or by an oncogenic activating mutation in JAK2 (V617 F) often present in myeloproliferative neoplasms [155]. Interestingly, the *JAK2* gene is on the same chromosome as, and can be co-amplified with, *PD-L1* and *PD-L2* to further enhance their expression [141].

Other mutations or epigenetic changes may reduce or prevent PD-L1 expression. IFN-γ can upregulate PD-L1 in tumours but also has anti-tumour effects, such as increasing Ag presentation and the release of T-cell attracting chemokines [156]. Therefore, mutations disrupting IFN-γ signalling could help tumours escape immune attack despite reducing PD-L1 levels. Indeed, mutations that inactivate JAK1 or JAK2 have been found in human melanoma and colorectal cancer that prevent IFN-γ signalling, preventing PD-L1 expression and a lack of response, or acquired resistance, to anti-PD-1 therapy [156][157]. Similarly, in mice, deletion of genes required for IFN-γ signalling (*Ifngr1, Ifngr2, Stat1, Jak1* and *Jak2*) reduces the sensitivity of melanoma to PD-1/PD-L1 blockade [158]. The detection of these various mutations may allow the identification of patients that are likely to respond to PD-1/PD-L1 blockade.

A cancer may be negative for PD-L1 expression but express PD-L2. PD-L1 is more commonly expressed in tumours, but PD-L2 is up-regulated in certain tumour types, including esophageal squamous cell carcinoma and B-cell lymphoma [159,160]. PD-L2 positivity in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) has been reported to predict response to pembrolizumab in patients negative for PD-L1 [161]. Patients with tumours positive for both PD-L1 and PD-L2 had increased clinical responses to pembrolizumab compared with those with PD-L1 expression alone (27.5% and 11.4%, respectively) [161]. PD-L2 and PD-L1 can also be expressed by APCs in SLTs, and activated tumour-specific PD-1$^+$ T-cells may be suppressed in these organs rather than in the TME [13]. Thus, even tumours with no PD-L1 or PD-L2 might still respond to PD-1/PD-L1 blockade. A more in-depth evaluation of PD-L1/PD-L2 expression may therefore improve the ability to predict response to anti-PD-L1 or anti-PD-1 therapy.

Clearly patients in whom PD-1 is playing no role in the suppression of tumour-specific T cells will show innate resistance to PD-1/PD-L1 blockade. However, this might not exclude the use of PD-1/PD-L1 blockade as part of a combination therapy. 'Cold tumours' may not express PD-1 ligands because they lack the inflammatory cell infiltrate required to induce their expression. Therapies that enhance immune cell infiltration of the TME may induce the intratumoural expression of PD-L, such that the inclusion of PD-1/PD-L1 blockade in the treatment plan could enhance the overall anti-tumour response. Combination therapies be will discussed in Section 7.

6.4. Antigen presentation by tumour cells and sensitivity to CTL killing

High tumour mutational burden is likely to increase neo-Ag load, but the efficiency with which tumours present these neo-Ags on MHCI to T-cells will affect responses to PD-1/PD-L1 blockade. Tumours that present poorly will not be detected by anti-tumour CTLs. Tumour cells can down-regulate expression of MHCI:Ag complexes to prevent recognition by CTLs [162]. Immunoediting during tumour development can drive the emergence of tumour cells with reduced MHCI expression [163], or select for mutations that generate neo-Ags that bind poorly to MHCI [164]. In addition, resistance to pembrolizumab is seen in tumours that contain, or acquire, mutations in beta-2-microglobulin, a protein vital for Ag presentation by MHCI [100,157,165,166]. A study of more than 1500 cancer patients, revealed a significant association between resistance to checkpoint blockade (anti-CTLA-4 or anti-PD-1/PD-L1 or both) and homozygosity in one or more of the three highly variable genes (*HLA-A*, *HLA-B* and *HLA-C*) that encode MHCI [167]: these genotypes are likely to restrict neo-Ag presentation to CTLs. Interestingly, in a separate study of melanoma patients, and in contrast to responses to anti-CTLA-4, positive responses to anti-PD-1 were associated with expression of MHCII, but not MHCI, proteins by the tumour and with the presence of IFN-γ-mediated gene signatures [168].

Checkpoint blockade therapy will put selective pressure on tumours to acquire immune evasion strategies. Elimination of the cells presenting neo-Ags recognised by CTLs may allow the outgrowth of malignant cells that are no longer recognised. Therefore, PD-1/PD-L1 blockade therapy may be successful in patients for a period of time before the stimulated T-cells no longer recognise the tumour cells. Anagnostou and colleagues used whole exome sequencing of tumours from patients with NSCLC who had acquired resistance to treatment with PD-1/PD-L1 blockade and identified that these tumours had lost mutations associated with neo-Ag generation [169]. In mice, PD-1/PD-L1 blockade can limit intratumoral diversity and enhance immunoediting [170,171], and in two patients with Merkel cell carcinoma, whose tumours had relapsed after responding well to immunotherapies including PD-1 or PD-L1 antibodies, transcription of

genes encoding MHCI had been lost [172]. Promoting T-cell priming throughout the course PD-1/PD-L1 blockade therapy may help prevent patients from developing acquired resistance by inducing a more diverse population of CTLs in the TME.

Sensitivity to CTL attack is not solely determined by MHCI/Ag presentation. Recent work has revealed that deficiency in tumour cells of a chromatin remodelling complex SWI/SNF can enhance responses to PD-1/PD-L1 blockade by increasing the sensitivity of tumour cells to CTL killing [173,174]. In clear cell renal carcinoma, loss-of-function mutations in PBRM1, which encodes part of the SWI/SNF complex, were associated with clinically beneficial responses to anti-PD-1 monotherapy or to combination therapies including anti-PD-1 or anti-PD-L1 with anti-CTLA-4 [174]. Mutation of genes encoding proteins found in this complex sensitised melanoma cells to CTL-mediated killing in mice and synergised with anti-PD-1/anti-CTLA-4 [174]. The reason for this is not entirely clear, although disruption of the SWI/SNF complex increased tumour cell sensitivity to IFN-γ to enhance secretion of chemokines that attract effector T-cells [173].

Thus, the presentation of tumour Ag, and the sensitivity of the tumour cells to CTL attack, influences resistance to PD-1/PD-L1 blockade.

6.5. PD-1-independent mechanisms of T-cell suppression or evasion

Inhibition of T-cells via PD-1 may be relieved by PD-1/PD-L1 blockade but this will not be effective if the tumour has, or acquires in response to treatment, an alternative way of evading or suppressing tumour-specific immune responses. It is unlikely that optimal tumour growth and survival will be achieved by relying on a single mechanism to T-cell suppression. Studies in mice have revealed a whole host of PD-1-independent immunosuppressive mechanisms that malignant cells or the TME can evolve to evade or suppress T-cell attack. These include harnessing the immunosuppressive properties of Tregs or myeloid derived suppressive cells; exploiting other immune checkpoint proteins; interfering with T-cell survival; or manipulating tumour-associated macrophage (TAM) abundance and function [175]. As well as shaping the immunosuppressive TME, TAMs can limit the efficiency of PD-1/PD-L1 blockade by using Fc receptors to directly remove anti-PD-1 antibodies from CD8 + T-cells shortly after they have bound to PD-1 [176]. Therefore, in addition to suppressing T-cell anti-tumour responses, myeloid cells in the TME can directly limit the efficacy of anti-PD-1 antibodies.

Other myeloid cells have also been linked to responses to PD-1/PD-L1 blockade. High levels of circulating CD14 + CD16-HLA-DR^{hi} classical monocytes prior to treatment is a good predictor of progression-free and overall survival after PD-1/PD-L1 blockade in melanoma patients [177]. The reason for this association remains to be defined, but quantifying circulating monocytes, alongside other analyses, might help to identify patients that are likely to be resistant, or responsive, to PD-1/PD-L1 blockade.

In recent years, it has become clear that tumour cells develop altered metabolism to allow sustained uncontrolled growth in a nutrient-poor environment [178]. Tumour cells can outcompete T-cells for glucose to reduce glycolytic activity and IFN-γ production by T-cells [44]. PD-1/PD-L1 blockade can restore T-cell glycolysis, and it will be interesting to see if hypoxic tumours, such as large tumours with necrotic cores, contain T-cells that do not respond well to PD-1/PD-L1 blockade due to a lack of nutrients. Indeed, in pre-treatment melanomas, genes associated with hypoxia are reportedly more highly expressed in the tumours of patients that subsequently respond poorly to anti-PD-1 antibodies compared to tumours from patients that subsequently respond well to this therapy [110]. Combination therapies which target the PD-1 axis and tumour metabolism may improve PD-1/PD-L1 blockade efficacy [179].

6.6. Types of T-cells and their response to PD-1/PD-L1 blockade

PD-1/PD-L1 blockade is intended to reinvigorate exhausted tumour-specific CD8 + T-cells. However, several different populations of CD8 + T-cells exist in cancer patients, including naïve, effector (T_{EFF}), effector memory (T_{EM}), resident memory (T_{RM}), central memory (T_{CM}) and exhausted (T_{EX}). It is becoming clear that they can respond differently to PD-1/PD-L1 blockade. During chronic LCMV infection in mice, PD-1/PD-L1 blockade results in the expansion of LCMV-specific CD8 + T-cells with a gene signature that resembles a progenitor-like cell, and which can self-renew and give rise to terminally differentiated CD8 + T-cell progeny in response to PD-1/PD-L1 blockade [180]. In mouse tumours, progenitor-like PD-1 + CD8 + T cells have also been identified that proliferate and differentiate in response to blockade of PD-1, or PD-1 and CTLA-4, and which are required for optimal tumour control induced by dual checkpoint blockade [181,182]. Kurtulus and colleagues defined a similar population of cells in mouse tumours when PD-1 plus another immune checkpoint protein, Tim-3, were blocked, although it was PD-1-negative progenitor-like CD8 + T cells that expanded under these conditions and were required for therapeutic responses [183]. Similar observations have been made in the context of chronic viral infection, with one study showing that PD-1/PD-L1 blockade results in the selective expansion of CD8 + T-cells expressing SIRPα [184] (an inhibitory receptor for CD47), while another reported the expansion of “progenitor exhausted” Tim3- CD8 + T-cells but not “terminally exhausted” Tim3 + CD8 + T-cells [182]. In all these studies, the transcription factor Tcf1/Tcf7 was found to be of key importance in the generation and/or maintenance of the cells [180–184]. Tcf1/Tcf7 + memory-like CD8 + T cells have been detected in human tumours, and their increased frequency can predict positive responses to checkpoint blockade in melanoma patients [165,181–183]. In NSCLC samples, subsets of intratumoural CD8 + T cells, referred to as ‘PD-1 high’ or ‘dormant’, are also predictive of response to PD-1/PD-L1 blockade [185,186], and it remains to be seen if they resemble the Tcf1/Tcf7 + CD8 + T cells present in melanoma.

Clinical responses to PD-1/PD-L1 blockade will be influenced by the TCR specificities of the reinvigorated T-cells, but other T-cell proteins are likely to be required. For example, in mice carrying tumours generated using the CT26 colon cancer cell line, responses to anti-PD-L1 are dependent on signalling through CD28 [22]. Tumours regressed in nearly all mice treated with anti-PD-L1, but if a CD28 blocker was included then tumours continued to grow in 80% of the mice. In mice treated with anti-PD-L1, intratumoural activated PD-1 + CTLs highly expressed CD28, suggesting that it was the T-cells responding to PD-L1 blockade that required CD28 expression. This study also reported that 20–90% of CTLs in human NSCLCs are CD28 + : this variation in CD28 expression may have value in predicting which patients are likely to respond to anti-PD-1/PD-L1 therapies.

Changes in intratumoural and circulating T-cell populations induced by PD-1/PD-L1 blockade have been tracked in cancer patients [187–189]. Based on analysis of tumour biopsies from 53 pembrolizumab-treated melanoma patients, Ribas and colleagues reported that the most prominent cell type to expand in the tumour following therapy is the CD8 + memory T cell [188]. Others have reported the expansion of exhausted-like terminally differentiated CD8 + T cells (Eomes + T-bet + PD-1 +) in tumours from anti-PD-1-treated melanoma patients [63,166], and Eomes^{hi} T-bet^{lo} PD-1 + CD8 + T-cells in peripheral blood become invigorated and proliferative in most melanoma patients treated with pembrolizumab [189]. TCR sequencing revealed that responding T-cell clones detected in the blood were also present in the tumour. Interestingly, it seems that failure to develop a clinical response to pembrolizumab treatment may not be solely due to the inability to reinvigorate T-cells, but rather the extent of this reinvigoration relative to the overall tumour burden in the patient [189]. Remarkably, in 8 of 27 patients with resectable stage III/IV melanoma, a single dose of neoadjuvant anti-PD-1 antibody has been shown to

reinvigorate exhausted T-cells in blood within one week, and, within three weeks, induce the accumulation of exhausted T-cells and major pathological responses in the resected tumour [166]. As previously [94,109], these changes were associated with a pre-treatment and post-treatment transcriptional signature enriched for T-cell activation, and, more importantly, with an impressive extension of disease-free survival [166].

Thus, in addition to intratumoural T-cell frequency, antigen-specificity and entry into the TME, predicting whether a patient responds to PD-1/PD-L1 blockade needs to include an understanding of the types of CD8 + T-cells that are present in the tumour and the circulation before, during and after treatment. Therapeutics that modify the abundance and phenotype of the key responsive CD8 + T-cell populations could potentially synergise with PD-1/PD-L1 blockade in combination therapies. Such approaches would be particularly effective if they lead to the generation of long-lived anti-tumour memory T-cells because these cells are likely to be key for durable and curative anti-tumour responses.

6.7. Influence of the microbiome

It is emerging that the microbiome influences responses to PD-1/PD-L1 blockade therapy. Studies on patients with melanoma or NSCLC have revealed associations between responses to PD-1/PD-L1 blockade and the presence of certain bacterial species in the oral or gut microbiome, and antibiotics can reduce the clinical benefit of PD-1/PD-L1 blockade therapy in cancer patients and mice [190–194]. Compared to faecal microbiota from non-responding patients, when faecal microbiota from patients who responded to PD-1/PD-L1 blockade was transplanted into germ-free mice it increased anti-tumour T-cell responses, enhanced recruitment of T-cells into the TME, and led to greater efficacy of PD-1/PD-L1 blockade [191]. Moreover, a cocktail of 11 specific bacterial strains from the faeces of healthy humans has been formulated that can enhance the anti-tumour efficacy of ICIs in mice, most likely due to their ability to induce IFN-γ-producing CD8 + T-cells in the intestine [194].

The influence of the microbiome adds further complexity to the issues of resistance and responsiveness to PD-1/PD-L1 blockade therapy. Defining the mechanisms and microbial components underlying this effect may provide additional biomarkers for patient stratification.

7. Overcoming resistance by combining PD-1/PD-L1 blockers with other therapies

It is clear that many challenges need to be overcome if PD-1/PD-L1 blockade therapy is to have clinical impact in more patients. The inclusion of anti-PD-1 or anti-PD-L1 in combination therapies is the principal way it is hoped that this can be achieved and there have been some significant clinical and experimental advances in this area in recent years. Provided side effects can be controlled, it is likely that combination therapies will be important in improving response rates to all IO agents, including those targeting the PD-1/PD-L axis. Experiments in mice have identified many approaches that sensitise tumours to PD-1/PD-L1 blockade, or in which the anti-tumour activity of other therapies is augmented by PD-1/PD-L1 inhibitors. Remarkably, there are over 900 clinical trials ongoing or recruiting in which PD-1/PD-L1 blockade is being used in a combination approach [195], and a number have already received FDA approval (Fig. 4).

7.1. Targeting two immune checkpoints

In theory, inhibition of CTLA-4 should increase the number of effector T-cells generated in SLTs and reduce Treg abundance in the TME, while anti-PD-1/PD-L1 therapy should prevent effector T-cells from being inhibited by malignant cells and stromal cells in the TME that express PD-Ls. In fact, anti-PD-1/PD-L1 and anti-CTLA4 therapies appear to target separate populations of T-cells: those activated by PD-1/PD-L1 blockade have been discussed in Section 6.6; anti-CTLA4 antibodies, in addition to depleting Tregs, induce the expansion of a subset of ICOS + Th1-like CD4 + T-cells [63]. Thus, anti-CTLA4 antibodies should augment clinical response to PD-1/PD-L1 blockade, and vice versa. The impact of combining these two therapies was first explored in melanoma and NSCLC [196–199].

In a phase I trial, 53 patients with advanced stage III or IV melanoma were treated with nivolumab and ipilimumab [198]. Results were promising: tumours regressed by ≥80% in 53% of patients. Five patients had a complete response. Treatment-related adverse events were reported as manageable and reversible with treatment, and there were no treatment-related deaths. Recently, however, the 3-year overall survival rates from this trial have been published: 58% for patients on the combination therapy; 52% for patients receiving nivolumab alone; and 34% when only ipilimumab was administered [88]. Thus, compared to nivolumab alone, combination therapy only resulted in a small increase in survival at 3 years. In a similar study, patients with unresectable or stage IV melanoma were randomised into three treatment groups: nivolumab alone, ipilimumab alone, or nivolumab and ipilimumab [197]. ORRs were 43.7%, 19% and 57.6%, respectively. However, toxicities were greater in the combination therapy group with 55% of patients experiencing grade 3/4 treatment-related adverse events, compared with 16.3% in the nivolumab only group and 27.3% in patients that only received ipilimumab. Nonetheless, these trials led to FDA approval for this combination therapy for melanoma in 2015 (Fig. 4).

This combination therapy has subsequently been approved for patients with advanced renal cell carcinoma and certain types of metastatic colorectal cancer (Fig. 4), and patients with renal cell carcinoma receiving nivolumab plus ipilimumab reported better health-related quality of life than patients given the VEGF inhibitor sunitinib [200]. Nivolumab plus ipilimumab has been tested in NSCLC patients, with encouraging results [196], and similar combinations are currently being trialled in other cancers. However, high toxicity remains a concern [78]. Moreover, recent work indicates that combining inhibitors of CTLA-4 and PD-1 might compromise anti-tumour immunity when tumour burden is low because it over-activates partially exhausted anti-tumour T-cells to induce activation-induced IFN-γ-dependent death [201]. Therefore, combining ICIs will not be effective against all tumours, and greater understanding is needed to allow patients to be identified that will benefit from this approach. This is particularly important given the increased severity and frequency of side effects.

Antibodies targeting CTLA-4 or the PD-1/PD-L1 axis are currently the only ICIs approved for use in humans, but other immune checkpoints are under investigation as potential targets, with promising results in mice (Fig. 4). For example, TIGIT protein is found on a number of immune cells, including CD8 + T-cells, NK cells, and Tregs, and has inhibitory roles that can help tumours escape immune responses [202]. In a murine glioblastoma model, combining anti-PD-1 and anti-TIGIT antibodies increased levels of CD8 + T-cell infiltration and overall survival [203]. Similar results were seen using anti-PD-L1 and anti-TIGIT antibodies in other mouse models of cancer, with TIGIT blockade inducing potent NK cell-dependent tumour-specific T-cell responses [204]. Blocking other immune checkpoints, such as B7S1 [205], NKG2A [206], LAG3 [207], CD39 [208], or the innate immune checkpoint CD47 [209], has also been found to augment anti-tumour responses elicited by anti-PD-1/PD-L1 antibodies in mice, while activating/targeting T-cell co-stimulatory molecules, such as CD40 [122,210,211], GITR [212], or 4-1BB (CD137) [213] can have a similar effect (Fig. 4). Further work is needed to understand relevance to human cancer, but including other ICIs, or antibodies targeting T-cell co-stimulatory molecules, clearly has potential to broaden the impact of therapeutics blocking the PD-1/PD-L axis. Interestingly, it has recently been reported that T-cells in melanomas from patients unresponsive to

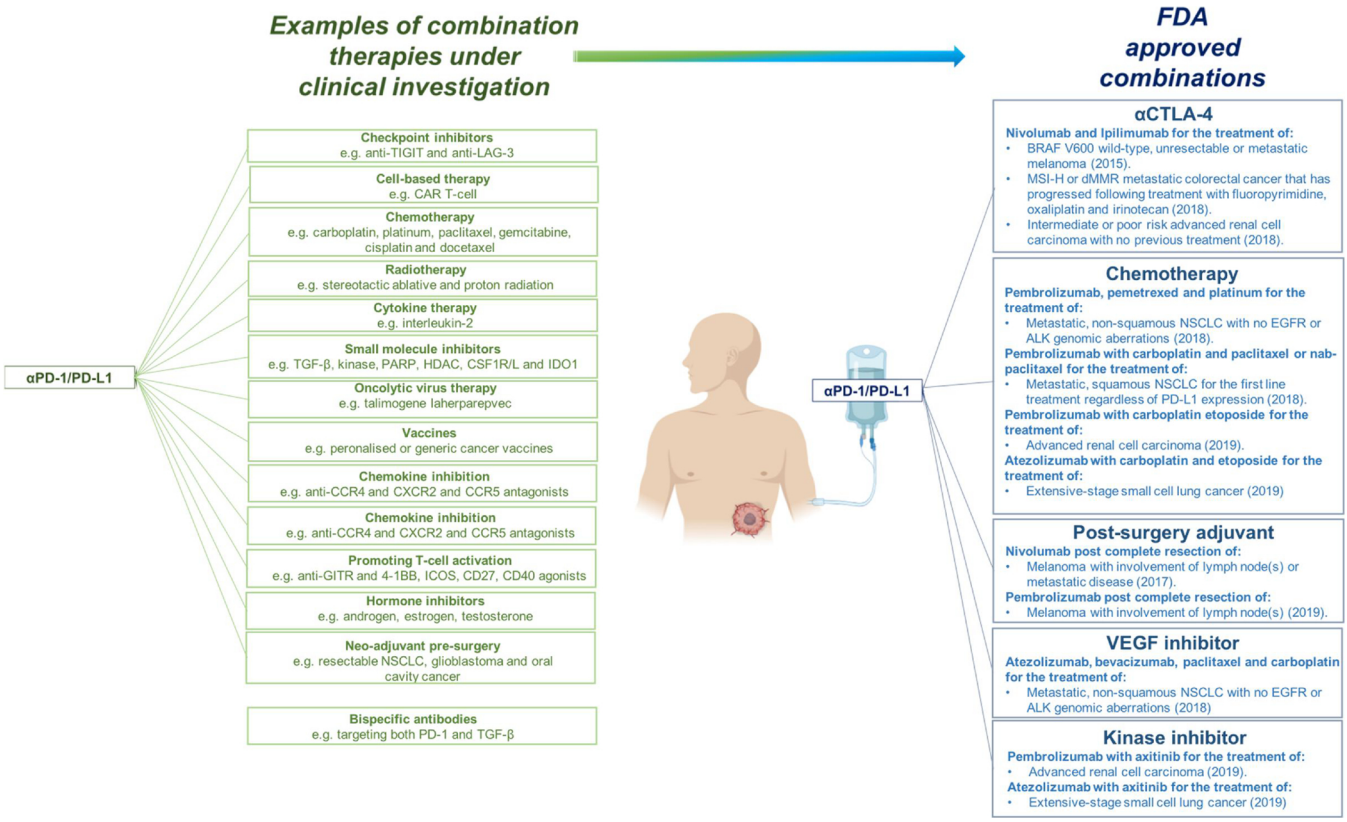

Fig. 4. Combination therapies involving anti-PD-1 or -PD-L1 antibodies that are FDA-approved or in clinical trials. Right: Combination therapies with FDA approval: cancer type and year of approval are shown. **Left**: Therapies currently in clinical trials in combination with anti-PD-1 or -PD-L1 antibodies: examples are provided of each therapy. Bi-specific antibodies are also included. For more information search clinicaltrials.gov using 'PD-1' or 'PD-L1'.

anti-PD-1 alone or with anti-CTLA4 often express other immune checkpoints, such as LAG3 or TIGIT [110].

7.2. Combining PD-1/PD-L1 blockade with chemotherapy, radiotherapy or surgery

Combination strategies that increase tumour immunogenicity might sensitise tumours to PD-1/PD-L1 blockade or other IO therapies. Therapies that induce PD-L1 or PD-L2 on tumour cells that are otherwise PD-L-negative might be more effective if the PD-1/PD-L axis is simultaneously blocked. Certain chemotherapeutics can induce immunogenic cell death releasing tumour Ags and damage-associated molecular patterns (DAMPs) that activate TLRs [214–217]. This can activate anti-tumour T-cells that infiltrate the TME and contribute to the efficacy of the chemotherapeutic. This will be dampened if PD-1/PD-L or other immune checkpoints are active in the tumour but enhanced if checkpoint blockade therapy is included. This has been successful in the clinic [218,219] and chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel) with pembrolizumab has received FDA approval as a first-line treatment for metastatic squamous NSCLC (Fig. 4). Many clinical trials using chemotherapy with PD-1/PD-L1 blockade are underway in various cancer types, while others are combining PD-1/PD-L1 blockers with small molecule inhibitors of key oncogenes or signalling molecules, such as BRAF in melanoma, RET/PDGFR in renal cell cancer, VEGF-A in NSCLC, MEK in melanoma and NSCLC, and PI3Kγ in several cancer types [150,220] (Fig. 4). The efficacy of some small molecule inhibitors is, like chemotherapy, thought to depend, at least in part, on adaptive immune responses and it might be possible to enhance these responses by using checkpoint blockade. The results of all these trials are eagerly anticipated.

Radiotherapy is able to enhance many key immune processes in tumours, including the release of inflammatory mediators and immune cell infiltration of the TME; the presence of MHC:tumour Ag complexes; cross presentation of tumour Ags in SLTs; and PD-L1 expression in the TME [221–223]. Anti-PD-L1 antibodies and ionizing radiation synergise to reduce tumour growth in murine breast carcinoma models [224,225], and anti-PD-1 or anti-PD-L1 antibodies can augment anti-tumour responses induced in mice by radiation plus CTLA-4 blockade [226]. Radiotherapy is known to elicit anti-tumour activity in non-irradiated distant tumours, a phenomenon known as the abscopal effect [227]. A combination of radiation and PD-1/PD-L1 blockade in mouse models of melanoma or renal carcinoma significantly reduced the size of metastatic tumour deposits outside the radiation field compared with mice treated with either therapy alone [228]. Thus, PD-1/PD-L1 blockade, and other immunotherapeutics [229], can augment the abscopal effect. Moreover, in a recent study, radiotherapy was combined with DC-stimulating cytokine Flt3L and TLR3 agonist poly-ICLC to enhance cross-presentation of tumour Ag by DCs to CD8 + T-cells in mice and patients with indolent non-Hodgkin's lymphoma [230]. This approach, referred to as *in situ* vaccination, increased the likelihood of remission. PD-1 + CD8 + T-cells were present in non-responding patients, and tumours in mice became responsive to PD-1 blockers. Combining radiotherapy with PD-1/PD-L1 blockade and *in situ* or conventional vaccination strategies might have significant therapeutic potential in humans.

Recently, the impact of PD-1/PD-L1 blockade as a neoadjuvant has been explored in patients with surgically resectable tumours. In NSCLC, neoadjuvant nivolumab had few side effects and, in 9 of the 21 patients, had induced major pathological responses in the resected tumours [231]. Two trials in small numbers of melanoma patients using neoadjuvant nivolumab, or nivolumab plus ipilimumab, gave encouraging patient outcomes, although significant toxicities were associated with the nivolumab/ipilimumab combination [232–234]. Pembrolizumab and nivolumab have yielded positive immunological

outcomes as neoadjuvants in patients with resectable glioblastoma [235,236] and, in one study [235], patients receiving pembrolizumab before and after surgery survived longer than those who only received pembrolizumab after surgery. PD-1/PD-L1 blockade is also effective in the adjuvant setting and nivolumab and pembrolizumab have both received FDA approval in this context for treating patients with resectable melanoma (Fig. 4). Future studies will no doubt build on these encouraging clinical outcomes.

7.3. PD-1/PD-L1 blockade and oncolytic viruses

Oncolytic viruses may also have therapeutic potential in combination with PD-1/PD-L1 blockade. They have specificity for tumour cells often because the mechanisms exploited by tumours to prevent them from being targeted by immune cells can make them more vulnerable to viral infection [237,238]. Oncolytic viruses can induce tumour cell lysis leading to the release of neo-Ags and the induction of virus- and tumour-specific T-cells which infiltrate the TME and destroy virus-infected malignant cells. This will be less effective if PD-Ls are present, or are induced by the virus, on tumour cells or cells in the TME. Thus, PD-1/PD-L1 blockade therapy and oncolytic virus infection may synergise to enhance cancer elimination. In mice, oncolytic viruses can sensitise gliomas or triple-negative breast cancer to checkpoint blockade therapy [239–241]. Moreover, a recent clinical trial involving 21 patients with advanced melanoma combined pembrolizumab with infection by the oncolytic virus talimogene laherparepvec, a version of herpes simplex virus 1 engineered to express the human version of GM-CSF [242]. The ORR was 62%, and there was evidence of increased CTLs and IFNγ-induced gene expression in the TME of those that responded to treatment.

7.4. Other effective pre-clinical combination therapies involving PD-1/PD-L1 blockade

In addition to the approaches discussed above, work in mice has revealed many other ways that anti-tumour responses to PD-1/PD-L1 blockade can be enhanced, or that PD-1/PD-L1 blockade can enhance other therapeutic approaches, and a selection of these are summarised here. Many are already moving into the clinic (Fig. 4). For example, responsiveness to PD-1/PD-L1 blockade can be enhanced by manipulating chemokines or chemokine receptors [243–247], reactivating MYC-dependent apoptosis [248], blocking galectin-3 [249], depleting CD25 + T-cells with an IL-2 receptor-targeted toxin [250], or inhibiting CDK4/6, TNF-α or its receptor TNFR1 [132,251]. The resistance of certain brain tumours to PD-1/PD-L1 blockade can be reversed by the adoptive transfer of haematopoietic stem/progenitor cells: these cells are thought to generate APCs that increase Ag presentation to CD8 + cells [252]. Nanoparticles loaded with TLR agonists or chemotherapeutics can synergise with PD-1/PD-L1 blockade to elicit enhanced anti-tumour responses [253,254]. Based on the SWI/SNF studies described above [173,174], small molecule inhibitors of chromatin remodelling have been found to synergise with PD-1/PD-L1 blockade to enhance tumour attack [255], while drugs that modify the metabolic pathways of tumour cells also increase responses [179]. Treg depletion with checkpoint blockade has proved effective in mouse models of claudin-low breast cancer [256], while faecal transplants, or other ways of manipulating the microbiota, is being explored as a way of improving responses to PD-1/PD-L1 blockade in humans [190–194]. The TGF-β pathway is another potential target. Certain human tumours that exclude T-cells and are resistant to PD-1/PD-L1 blockade are surrounded by peritumoural fibroblasts with gene expression signatures indicative of TGF-β signalling: interfering with TGF-β or its receptors can sensitise tumours in mice to PD-1/PD-L1 blockade and other ICIs [130,131,257]. Bifunctional fusion proteins blocking PD-L1 and TGF-β have entered clinical trials [258]. In addition, blocking PD-1, or other immune checkpoints, can enhance responses to CAR T-cells and increase the effectiveness of cancer vaccines that induce or re-educate anti-tumour CTLs [9,259–261]. Given that defective DNA repair is associated with increased responses to PD-1/PD-L1 blockade [100,101], drugs that target DNA repair pathways might be expected to enhance the efficacy of ICIs. Indeed, clinically-approved PARP inhibitors, which interfere with the sensing of DNA damage and lead to single-strand and double strand breaks in DNA, can upregulate PD-L1 expression and PD-L1 blockade enhances their ability to suppress tumour growth in mouse models of breast and small cell lung cancer [262,263]. Similarly, PARP inhibitor niraparib was found to upregulate interferon pathways in tumours, enhance T-cell recruitment into the TME, and synergise with anti-PD-1 antibody in anti-tumour responses in a variety of mouse models [264]. Clinical trials are underway combining PARP inhibitors and PD-1 inhibitors [265], and recent studies showing that prexasertib-mediated inhibition of CHK1 kinase (which coordinates the DNA damage response) also synergises with PD-L1 blockers in mouse small cell lung cancer models [263] may pave the way for other combination therapy trials in humans.

8. Conclusions and future perspectives

The immune system contains everything needed to prevent tumour formation, so tumours that do develop must be capable of inhibiting or evading immune destruction. This can be achieved by exploiting natural mechanisms of immune suppression, such as those mediated by immune checkpoint proteins. ICIs aim to reverse this exploitation and reinvigorate immune cells so that they can attack cancer cells. Many years of research into the role of the PD-1/PD-L axis in T-cell regulation and cancer immunosuppression have culminated with the development of PD-1/PD-L1 ICIs for the treatment of cancer in humans. In a variety of cancer types, albeit in a small proportion of patients, clinical outcomes to monotherapy have been dramatic with durable, even curative, responses against advanced metastatic disease. Safety profiles are acceptable, often better than those seen with other drugs. These clinical results have been, without question, the key findings in the field. They have extended life expectancy for many patients and catalysed an explosion of preclinical research and clinical trials that is not just focussed on PD-1/PD-L1 but which incorporates many other immune checkpoints and a whole variety of other immunotherapeutic approaches. In the past, there have been many ‘false dawns’ in the clinical application of cancer immunology research: the outcomes of clinical trials of PD-1/PD-L1 blockers have resoundingly established immunotherapy into mainstream cancer treatment alongside chemotherapy, radiotherapy and surgery. Nonetheless, from the very first clinical trial it was clear that there needed to be a greater appreciation of how PD-1/PD-L1 blockade was working; that potentially responsive patients would need to be identified before or shortly after treatment was commenced; and that innate and acquired resistance would be major challenges.

In the intervening years there have been concerted efforts to address these key weaknesses and progress has been rapid. There is a now a much clearer picture of the types of T-cells, including TexS cells and progenitor-like CD8 + T-cells, that respond to PD-1/PD-L1 blockers in patients to drive positive clinical outcomes. Important advances have been, and are continuing to be, made in the identification of biomarkers present in blood and/or tumour [266]. Combining existing pre-treatment biomarkers, and incorporating others from future studies, could enable the stratification of patient cohorts into responders, non-responders and potential responders. Monitoring biomarkers during treatment will provide further insights that could be used to inform patient treatment. They might result in additional ‘tissue/site agnostic’ approvals for PD-1/PD-L1 blockers akin to the current one based on dMMR or MSI-H rather than tumour location [101] but this depends on whether specific panels of mutations or biomarkers can be successfully identified that provide robust guidance for clinicians. These approaches will need to be carefully established for each tumour type and must avoid potentially responsive patients being excluded from treatment.

Cost and feasibility are other major issues. The ultimate goal is to develop cost-effective mutation/biomarker screening assays that are able to identify before, or shortly after, treatment (and with high levels of accuracy) those patients for whom therapeutics targeting PD-1/PD-L1 will result in a positive clinical outcome. This will not only have clear benefits for patient health, but will reduce the use of ineffective costly therapeutics, and avoid unnecessary treatment-related toxicities. Ultimately, this personalised medicine approach would be part of a much larger scheme that would allow suitable therapeutics to be identified for patients that are predicted to fail to respond to PD-1/PD-L1 blockers.

Another ultimate goal is to successfully tackle innate and acquired resistance so that the full clinical potential of PD-1/PD-L1 inhibitors can be unlocked and the proportion of patients benefitting from these drugs increased. Our rapidly growing appreciation of the mechanisms underpinning resistance will be enormously helpful and allow the development of logical intervention strategies. Combination therapies will be of central importance. Data from clinical trials, and the results of experiments in mice, are revealing a wide variety of ways that tumours can be sensitised to PD-1/PD-L1 blockade, and that PD-1/PD-L1 blockade can be used to enhance responses to existing anti-cancer treatments. Progress into the clinic has been quick and is likely to develop rapidly in the future (Fig. 4), not least of all because there are drugs already approved for use in humans that can be used to mimic successful experiments in mice. Ongoing combination therapy research holds huge potential for the future, and although not all will translate into clinical advances [267], it seems very likely that novel effective treatments will emerge that will substantially extend the reach of these, and other, ICIs.

The development of IO therapies, and particularly PD-1/PD-L1 inhibitors, have ushered in a new era of immunotherapy that has transformed the landscape of cancer treatment. The pace of progress is astonishing with experimental or clinical advances currently emerging almost on a daily basis. There are many reasons for optimism, and it is hoped that PD-1/PD-L1 blockade has the potential to become a highly effective therapeutic approach in many cancer patients, rather than just a few. PD-1/PD-L1 inhibitors are becoming firmly established in the oncologist's armoury and are likely to be one of the first of a new wave of drugs that successfully tackle cancers by exploiting the power of the immune system.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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