MINIREVIEW

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Anti-programmed cell death protein-1/ ligand-1 therapy in different cancers

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Immunologic checkpoint blockade with antibodies against the programmed cell death protein-1 (PD-1) or its ligand (PD-L1) is an effective method for reversing cancer immunosuppression and thereby promoting immune responses against several cancer types. Anti-PD-1 and anti-PD-L1 antibodies have resulted in long-term responses with minimal side effects in significant numbers of patients with melanoma, lung, kidney, bladder and triple-negative breast cancer, as well as in chemotherapy-refractory Hodgkin disease. There is already evidence from at least one randomised trial that anti-PD-1 therapy is superior to chemotherapy in the treatment of patients with metastatic melanoma, and two anti-PD-1 antibodies, pembrolizumab and nivolumab, have been approved by the US Food and Drug Administration for the treatment of patients previously treated for metastatic melanoma. It is anticipated that approvals by drug regulatory bodies will be forthcoming in several cancers in the next months.

Blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 or its ligand (PD-1/L1) represent a paradigm shift in immunotherapy for cancer, as it focus on the disinhibition of native immune responses instead of the prior focus in activation of the immune system with tumour vaccines or recombinant cytokines. Among the most promising approaches to activating therapeutic antitumour immunity is the blockade of immune checkpoints. CTLA-4 was the first negative regulatory checkpoint receptor to be clinically targeted. CTLA-4 is upregulated early during the T-cell activation and its expression dampens T cells by outcompeting CD28 in binding CD80 and CD86 (Linsley *et al*, 1994; Egen and Allison, 2002; Riley *et al*, 2002). Antibodies that block CTLA-4 enhance immune responses by activating effector T cells, but probably also by interacting with other immune cells such as regulatory T cells (Tregs), which exhibit immunosuppressive properties (Lenschow *et al*, 1996; Wing *et al*, 2008). The anti-CTLA-4 antibody ipilimumab (Yervoy; Bristol-Myers Squibb, Princeton, NJ, USA) showed a significant overall survival (OS) improvement in patients with advanced melanoma in two randomised phase III trials (Hodi *et al*, 2010; Robert *et al*, 2011), and was approved by the US Food and Drug Administration (FDA) and other drug regulatory bodies in 2011. The broad activation of the immune system and deregulation of an immunologic homoeostasis achieved by blocking CTLA-4 might be responsible for the development of inflammatory or autoimmune toxicities, reported in ~15% of the patients (Robinson *et al*, 2004).

In contrast, PD-1 appears to have a prominent role in modulating T-cell activity in peripheral tissues via interaction with its ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC). Programmed cell death protein-1 is an immune checkpoint receptor that prevents overstimulation of immune responses and contributes to the maintenance of immune tolerance to self-antigens (Freeman *et al*, 2000; Keir *et al*, 2006; Korman *et al*, 2006; Okazaki and Honjo, 2007). Upon antigen recognition, activated T cells express PD-1 on their surface and produce interferons that lead to the expression of PD-L1 in multiple tissues, including cancer (Ishida *et al*, 1992; Pardoll, 2012). Binding of PD-1 to its ligands limits effector T-cell activity, and therefore regulating detrimental immune responses and preventing autoimmunity (Topalian *et al*, 2012a). Programmed cell death protein-1 is not only induced on effector T cells but also on Tregs (Francisco *et al*, 2009), activated B cells and natural killer cells (Terme *et al*, 2011), suggesting its contribution to other important immune cell functions.

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Besides the interaction between CTLA-4 and PD-1 with their respective ligands, other costimulatory and inhibitory interactions regulate T-cell responses. Although not the focus of the current review, examples of promising inhibitors of immune checkpoint targets that are being pursued clinically using blocking antibodies include the lymphocyte-activation gene 3, the T-cell membrane protein 3 or the adenosine receptor A2aR.

REGULATION OF EXPRESSION OF PD-1 AND ITS LIGANDS

For PD-1 to inhibit effector T-cell function, engagement to its ligands is needed. Peripheral tissues that are able to express PD-L1 constitutively or upon interferon exposure include both haematopoietic and non-haematopoietic tissues. Numerous tumour types are also able to express PD-L1 (Zou and Chen, 2008), including urothelial, ovarian, breast, cervical, colorectal, pancreatic, gastric cancer, melanoma, glioblastoma and non-small-cell lung cancer (NSCLC), suggesting that the pathway may be involved in immune evasion by many different human cancers. Less is known about PD-L2, which is expressed on dendritic cells, macrophages, mast cells and B cells (Topalian *et al*, 2012b). In tumours, PD-L2 is upregulated on primary mediastinal B-cell lymphoma, follicular B-cell lymphoma and Hodgkin lymphoma (Rosenwald *et al*, 2003).

An important consideration is the mechanism that contributes to PD-L1 expression in the surface of tumour cells. Tumour PD-L1 membrane expression can be constitutive through oncogenic processes (Parsa *et al*, 2007; Pardoll, 2012) or induced by activated tumour antigen-specific T cells that produce interferons (Taube *et al*, 2012). Thus, the expression of PD-L1 can be considered a dynamic process during effector T-cell antigen recognition.

Recent data suggest that inducible PD-L1 expression may be most important for responses to PD-1 blockade therapy. In this scenario, the pre-existing presence of PD-1-positive T cells with tumour antigen specificity, which became inactivated upon PD-L1 engagement, is required for antitumour responses. This critical mechanism has been termed acquired immune resistance (Pardoll, 2012), and differs from other possible scenarios where tumour cells express PD-L1 in the absence of effector T cells or effector T cells are present but not properly activated and therefore not able to express PD-1 (Ribas and Tumeh, 2014).

Tumour infiltration with effector T cells and PD-L1 expression have been associated with objective responses to the anti-PD1 antibody pembrolizumab in biopsies of patients with advanced melanoma (Tumeh *et al*, 2014). A more clonal TCR receptor repertoire in the previous patients with clinical benefit has also been observed. Other work focused on inducible PD-L1 expressed by tumour-infiltrating T cells as predictive of response, which is also likely a reflection of the presence of tumour antigen-specific T cell-producing interferons. Although these findings strongly reinforce the concept of acquired immune resistance within the tumour, patients with PD-L1-non-expressing tumours could also potentially benefit from these agents, considering the previously described plasticity of the tumour with the upregulation of PD-L1, the heterogeneity of its expression levels (Taube *et al*, 2012) and the number of clinical reports where patients with both PD-L1-positive and -negative baseline tumour biopsies were associated with clinical benefit, although the latest group with less objective responses (Hodi *et al*, 2014; Kefford *et al*, 2014).

Programmed cell death protein-1/ligand-1 has also been studied as a prognostic biomarker in many different primary tumours, with equivocal results (Rosenwald *et al*, 2003; Parsa *et al*, 2007; Hino *et al*, 2010). Variations in cancer type, stage of cancer analysed, PD-L1 monoclonal antibody used for IHC staining, laboratory techniques for IHC staining and treatment history may have contributed to the diverse results.

TARGETING THE PD-1 PATHWAY

Several antibodies that inhibit the PD-1 pathway by blocking either PD-1 or PD-L1 are being developed for clinical use in a variety of tumour types and clinical settings (Table 1). These agents differ in structure and are generally classified into two groups: anti-PD1 and anti-PD-L1 antibodies. Antibodies that inhibit PD-1 block its binding to both PD-L1 and PD-L2, whereas anti-PD-L1 antibodies only block the PD-1:PD-L1 interaction and potentially the PD-1:CD80 interaction. Whether this difference affects clinical activity, organ-specific immune modulation or toxicity needs to be elucidated.

Regarding the anti-PD-1 antibodies, the fully human nivolumab (Bristol-Myers Squibb) and the humanised pembrolizumab (Merck, Whitehouse Station, NJ, USA) are IgG4 monoclonal antibodies that block the binding of PD-1 receptor to PD-L1 and PD-L2. Pembrolizumab has an optimised fragment crystallisable (fc) region that minimises antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). In contrast, the third anti-PD-1 antibody with more extensive clinical development pidilizumab (CureTech, Yavne, Israel) is an IgG1 antibody, which confers more ADCC and CDC. Antibodies in clinical development that target PD-L1 include MPDL3280A (Genentech, South San Francisco, CA, USA), MEDI4736 (MedImmune/AstraZeneca) and MSB0010718C (EMD Serono, Rockland, MA, USA), all of them IgG1 isotype. MPDL3280A and MEDI4736 have genetically modified Fc fragments to avoid ADCC, which is of particular importance for anti-PD-L1 antibodies as activated T cells readily express PD-L1 (Herbst *et al*, 2014). No data are available regarding the comparison of these agents and we will focus on describing the clinical data available for these antibodies in different tumours.

Table 1. Anti-PD-1/L-1 agents in clinical development

Agents	Prior names	Manufacturer	IgG type	Affinity
Nivolumab	MDX1106, BMS936558	BMS-ONO	IgG4 fully human AB	3 nM
Pembrolizumab	Lambrolizumab MK-3475	Merck	IgG4 engineered humanised AB	<100 pM
Pidilizumab	CT-011	CureTech	IgG1k humanised AB	–
BMS936559	MDX1105	BMS-ONO	IgG4 fully human AB	–
MPDL3280A	RG7446	Genentech/Roche	IgG1 engineered fully human AB	–
MEDI4736		MedImmune	IgG1 engineered fully human AB	–
MSB0010718C		Merck Serono	IgG1 fully human AB	–

Abbreviations: AB = antibody; IgG = immunoglobulin G; PD-1/L-1 = programmed cell death protein-1 or its ligand.

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PD-1 BLOCKADE EFFICACY: FIRST EVIDENCE OF CLINICAL ACTIVITY

The most extensive clinical experience with PD-1 antibodies has been obtained with both nivolumab and pembrolizumab, which have demonstrated highly durable response rates with acceptable toxicity in large phase I studies involving patients with advanced melanoma, NSCLC, renal cell carcinoma (RCC) and Hodgkin's disease, among others (Topalian *et al*, 2012b, 2014; Hamid *et al*, 2013a; Ansell *et al*, 2015).

Nivolumab was first evaluated in a phase I/II study in 296 patients with a variety of heavily pretreated malignancies including melanoma, NSCLC, prostate cancer, RCC and colorectal cancer. Patients received nivolumab at doses of 1–10 mg kg^{-1} of body weight every 2 weeks for up to 12 cycles until disease progression or a complete response occurred. No maximum-tolerated dose (MTD) was defined and only 14% of the patient experienced grade 3/4 drug-related adverse events. Cumulative response rates (all doses) were 18.4% (14 out of 76) among patients with NSCLC, 27.6% (26 out of 94) among patients with melanoma and 27.3% (9 out of 33) among patients with RCC (Topalian *et al*, 2012b). These results generated enthusiasm among oncologists and provided evidence of clinical activity in neoplasms classically considered non-immunogenic.

In parallel to the clinical development of nivolumab, the anti-PD-1 antibody pembrolizumab was similarly showing impressive tumour responses in a more restricted population of patients with advanced melanoma (Hamid *et al*, 2013a). Hamid *et al* (2013a) reported 135 patients with advanced melanoma being treated with three separate dosing strategies: 10 mg kg^{-1} of body weight every 2 or 3 weeks or 2 mg kg^{-1} every 3 weeks. Some patients were previously treated with ipilimumab. Adverse events were similar to those found in patients treated with nivolumab, including fatigue, rash, pruritus and diarrhoea. Response rates across all dose levels were 38%, with patients on the highest dose of pembrolizumab showing a response rate of 52%. Responses were durable, and the median progression-free survival (PFS) was longer than 7 months. A subsequent prospective, randomised analysis was performed using both 2 and 10 mg kg^{-1} doses given every 3 weeks to patients with ipilimumab-refractory advanced melanoma. The response rate was 26% at both doses and the safety profile was similar, making 2 mg kg^{-1} once every 3 weeks the recommended dose for further studies (Robert *et al*, 2014). An updated report on the phase I clinical trial (KEYNOTE-001) included the analysis of 411 melanoma patients treated across multiple dose levels. Median OS data was not available, but 1-year OS rate over all dose cohorts was 69% (Ribas *et al*, 2014a).

Pidilizumab has been more predominantly evaluated in haematologic malignancies. A phase I dose-escalating trial tested pidilizumab in 17 patients with refractory acute myeloid leukaemia, chronic lymphocytic leukaemia, Hodgkin and non-Hodgkin lymphoma or multiple myeloma and reported an acceptable safety profile, with no MTD defined and clinical benefit in 33% of the patients evaluated (Berger *et al*, 2008).

Targeting PD-L1 is a similarly promising approach to targeting PD-1. BMS-956559, although no longer under clinical development, was the first PD-L1 antibody to show durable tumour regressions in patients with a variety of solid tumours, mostly NSCLC and melanoma, and also RCC, colorectal, ovarian, pancreatic, gastric and breast cancer (Brahmer *et al*, 2012).

Other anti-PD-L1 antibodies such as MPDL3280A, MEDI4736 and MSB0010718C have also shown responses in early-phase clinical trials in a number of malignancies (Herbst *et al*, 2013; Heery *et al*, 2014; Segal *et al*, 2014). MPDL3280A phase I testing in patients with multiple histologies was well tolerated and did not reach a MTD (Herbst *et al*, 2013). Pharmacokinetic data supported dosing at 15 mg kg^{-1} every 3 weeks and activity was observed in multiple tumour types including NSCLC, RCC, melanoma, colorectal and gastric cancer. In phase I, another anti-PD-L1 antibody, MEDI4736, exhibited dose-dependent pharmacokinetics and yielded dose-dependent PD-L1 suppression (Fairman *et al*, 2014), with an acceptable safety profile, no MTD and evidence of clinical activity across multiple cancer types including melanoma, gastro-oesophageal, pancreatic cancer and head and neck squamous cell carcinoma (Segal *et al*, 2014). MSB0010718C dose-escalation trial was performed and investigators demonstrated that MSB0010718C could be safely administered in doses up to 20 mg kg^{-1} 2 weeks. Further development of this antibody is planned in patients with metastatic or locally advanced solid tumours. A summary of the phase II/III relevant clinical data for each agent is included in Table 2 and detailed below.

PD-1/L1 BLOCKADE IN DIFFERENT TUMOURS

Melanoma. Nivolumab was recently compared with dacarbazine in a phase III randomised double blind study in patients with treatment-naive BRAF wild-type advanced melanoma ($n = 418$) (Robert *et al*, 2014). The median OS was not reached for nivolumab *vs* 10.8 months for dacarbazine and 1-year survival rate was 73% *vs* 42%, respectively. This survival advantage was observed in both PD-L1-positive and -negative nivolumab-treated patients. Drug-related adverse events were more common in the dacarbazine-treated group. In a separate phase III trial, nivolumab was compared with investigator's choice chemotherapy in patients who had experienced progression on ipilimumab and resulted in an increased overall response rate from 11% to 32%, with less frequent high-grade adverse events (Weber *et al*, 2014). Nivolumab was approved in December 2014 for patients with advanced melanoma after disease progression to a previous therapy.

Table 2. Anti-PD-1/L1 agents: clinical data from phase II/III clinical trials

Anti-PD-1/L1	Phase	Pts	ORR	Disease	Grade3–4 AE	Median PFS (Mo)	1-year OS	Reference
Nivolumab	2	168	20	RCC	17	4.2 (10 mg kg^{-1})	NR	Motzer *et al* (2014b)
Nivolumab	2	117	15	NSCLC	17.1		41	
Nivolumab	3	418	40	MM	11.7	5.1	NR	Robert *et al* (2014)
Nivolumab	3	268	32	MM	9	NR	NR	Weber *et al* (2014)
Pembrolizumab	2	540	21 (2 mg kg^{-1}) 25 (10 mg kg^{-1})	MM ipi refractory	11 (2 mg kg^{-1}) 14 (10 mg kg^{-1})	2.9 (2 mg kg^{-1}) 2.9 (10 mg kg^{-1})	NR	Ribas *et al* (2014b)
Pidilizumab	2	103	5.9	MM		2.8	64.5	Atkins *et al* (2014)
Pidilizumab + Rituximab	2	30	66	FL	0	21.1	NR	Westin *et al* (2010)

Abbreviations: AE = adverse events (%); MM = metastatic melanoma; NR = not reported; NSCLC = non-small-cell lung cancer; ORR = overall response rate (%); PD-1/L-1 = programmed cell death protein-1 or its ligand; PFS = progression-free survival (months); Pts = patients; RCC = renal cell carcinoma; 1-year OS = years overall survival (%).

Phase II randomised clinical data with pembrolizumab have also been recently reported. At the 2014 Society for Melanoma Research (SMR) meeting, results on the primary end point of PFS comparing two dosing regimens of pembrolizumab with chemotherapy in patients with ipilimumab-refractory advanced melanoma were presented (Ribas *et al*, 2014b). Pembrolizumab provided significant improvements in PFS and durable objective responses while better preserving health-related quality of life compared with chemotherapy. Pembrolizumab received FDA approval in September 2014 for patients with melanoma previously treated with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Expansion cohorts of patients with metastatic melanoma treated with MPDL3280A resulted in an overall response rate of 26% (9 out of 35) and a 24-week PFS of 35% (Hamid *et al*, 2013b). MPDL3280A is currently being explored in combination with vemurafenib in advanced *BRAF*-mutated melanoma. The anti-PD-L1 antibody MEDI4736 is also currently under investigation in combination with dabrafenib and trametinib, or with trametinib alone, in subjects with metastatic melanoma with or without *BRAF* mutations, respectively.

Targeting T-cell activation at different stages of the immune response might lead to an increased efficacy in the clinical setting, while potentially delaying resistance to either agent. Combining the blockade of PD-1 and CTLA-4 in preclinical models achieved a more pronounced antitumour activity than blockade of either pathway alone and provided the rationale for further studying this combination (Curran *et al*, 2010). A phase I study evaluated the safety and efficacy of a concurrent regimen of ipilimumab and nivolumab in patients with advanced melanoma (Wolchok *et al*, 2013). Concurrent treatment was associated with an overall response rate of 40%, which seemingly exceeded the previously reported results with either agent alone (Hodi *et al*, 2010; Topalian *et al*, 2012b). However, 53% of the patients treated with the concurrent regimen had grade 3/4 treatment-related adverse events, which is higher than the previous rates among patients treated with ipilimumab or nivolumab alone. Whether the antitumour effect of both agents is more active than either agent alone is being addressed in a phase III clinical trial and results are eagerly awaited.

Non-small-cell lung carcinoma. Non-small-cell lung carcinoma is one great example of a cancer type that was not believed to be immune-responsive and where antibodies blocking the PD-1 checkpoint have shown therapeutic activity. Similar to melanoma, expression of immunoinhibitory molecules in the tumour microenvironment appears to be a relevant mechanism for immune resistance in NSCLC. Both PD-L1 and PD-L2 have been reported to be upregulated in NSCLC (Zou and Chen, 2008; Pardoll, 2012). Downregulation of components of the antigen-presenting machinery, particularly among smoking-associated lung cancer patients (Pleasance *et al*, 2010), appears to be another important immune resistance mechanism.

The initial signs of anti-PD-1 activity in patients with NSCLC were reported in the dose-escalation phase I clinical trial that evaluated nivolumab in different solid tumours (Topalian *et al*, 2012b). Expansion cohorts of patients with NSCLC showed significant responses and disease stabilisation in both non-squamous and squamous lung carcinoma. Durability of clinical responses, unique to immunotherapy, was unprecedented (median duration of response was 74 weeks and 1- and 2-year OS was 42% and 14%, respectively) (Brahmer *et al*, 2013). Of note, eight patients developed pneumonitis, three of which were grade 3/4. This organ-specific immune toxicity might be of particular importance in patients with NSCLC, as these patients may harbor some degree of pulmonary inflammation that might be enhanced upon PD-1 blockade.

Taken together, these encouraging results have led to the development of nivolumab in two separate phase III clinical trials. As a single agent, nivolumab is being compared with docetaxel in patients with non-squamous histology in the second- or third-line treatment setting and in patients with squamous cell histology after one prior platinum-containing regimen. In addition to multiple treatment-arm phase I trials where this antibody is being combined with various chemotherapy regimens, nivolumab is also being explored in the neoadjuvant setting in resectable NSCLC.

Regarding the testing of pembrolizumab in this patient population, a phase I clinical trial of previously treated patients with locally advanced or metastatic NSCLC was also recently reported. Enrolled patients had PD-L1 detected in their tumours by an immunohistochemical assay, although some patients with tumours without PD-L1 expression who had received at least two prior lines of therapy were also included. Treatment was generally well tolerated, although three patients experienced grade 3/4 drug-related pneumonitis. Robust antitumour activity was observed with a preliminary higher response rate (24%) for patients with PD-L1-positive tumours compared with PD-L1-non-expressing tumours (8%) (Garon *et al*, 2014).

Blocking anti-PD-L1 is a strategy extensively being evaluated in patients with NSCLC. MPDL3280A expansion cohort for previously treated patients with metastatic NSCLC observed an overall response rate of 24% (9 out of 37) in patients with both squamous and non-squamous histology, including several patients with rapid tumour shrinkage and additional patients with delayed responses after apparent radiographic progression (Spigel *et al*, 2013). There were no cases of grade 3/4 pneumonitis, suggesting a potentially more tolerable safety profile with anti-PD-L1 inhibitors in patients with NSCLC. Ongoing trials include a single-arm phase II study of MPDL3280A in chemonaive and prior platinum-based treated patients with PD-L1-positive tumours and a phase III efficacy and safety evaluation of MPDL3280A compared with docetaxel after failure of a platinum-containing chemotherapy regimen.

Preliminary clinical activity with MEDI4736 in patients with NSCLC has also been observed, with three partial responses and two additional patients showing tumour shrinkage not meeting partial response out of 13 patients evaluated (Brahmer *et al*, 2014). Same as with MPDL3280A, safety was acceptable and no grade 3/4 pneumonitis was observed. Several large combination trials are ongoing including the combination of an anti-EGFR and MEDI4736 in advanced NSCLC, its sequential administration after concurrent chemoradiation in stage III or *vs* placebo after a complete resection.

Renal cell carcinoma. Immunomodulation has classically been considered a therapeutic strategy for RCC, and cytokine-based immunotherapeutic agents such as IL-2 are associated with modest rates of highly durable responses. PD-L1 is increased in inflammatory conditions of the kidney and in RCC, as opposed to normal renal tissue, suggesting its role in negatively regulating T-cell function (Ding *et al*, 2005).

A randomised phase II clinical trial evaluated different doses of the nivolumab in patients with advanced RCC and observed long-lasting objective responses in 20–22% of the patients evaluated across all groups. Median OS was 18.2 months for the 0.3 mg kg^{-1} dose and was not reached for the 2 or 10 mg kg^{-1} doses (Motzer *et al*, 2014a). Results from a phase III study comparing nivolumab to everolimus in pretreated metastatic RCC could potentially lead to the registration of the anti-PD-1 antibody in this therapeutic setting. Nivolumab is currently being developed in combination with either sunitinib or pazopanib, with promising results in terms of efficacy but high level of toxicity (Amin *et al*, 2014). In the same trial, two separate arms evaluated the combination of ipilimumab plus nivolumab, with preliminary results suggesting the synergy of the combination, at the expense of significant toxicity (Hammers *et al*, 2014).

Pembrolizumab is currently being investigated in a phase I/II trial in combination with pazopanib in treatment-naive patients with metastatic RCC. Once the recommended phase II dose is determined, the potential for synergy combining both agents will be evaluated. Other antiangiogenics combined with pembrolizumab include axitinib.

The initial experience with MPDL3280A in RCC indicated the presence of responses across all dose, with some patients with RCC experiencing prolonged stable disease before experiencing tumour response. The 24-week PFS was 50% among the 39 patients evaluated for efficacy (Cho *et al*, 2013). MPDL3280A is currently being investigated as monotherapy or in combination with bevacizumab as compared with a control arm of sunitinib in patients with treatment-naive, locally advanced or metastatic RCC.

Triple-negative breast cancer. Programmed cell death protein-1/ligand-1 is expressed in 20% of triple-negative breast cancer (TNBCs), suggesting PD-L1 as a therapeutic target in TNBCs (Mittendorf *et al*, 2014). A phase Ib clinical trial with pembrolizumab in 27 patients with heavily pretreated recurrent or metastatic TNBC positive for PD-L1 achieved one complete response, four partial responses and seven cases with stable disease. Another complete response and two partial responses were obtained in a similar subgroup of patients with MPDL3280A.

Bladder cancer. A clinical trial involving patients with heavily pretreated metastatic bladder cancer selected to be PD-L1-positive based on an analysis of the PD-L1 expression on immune-infiltrating cells resulted in 10 out of 20 with a response (9 partial responses and 1 complete response). Response rates for patients with PD-L1-negative tumours have yet to be published (Powles *et al*, 2014). This study had a short follow-up of just 2.8 months, and further information will be needed to assess the benefits of PD-1/L1 blockade in patients with bladder cancer.

Haematologic malignancies. The importance of the PD-1 axis in leukaemias and lymphomas has been demonstrated in several different scenarios. Examples of haematologic malignancies that frequently express PD-L1 include adult T-cell leukaemia lymphoma (Kozako *et al*, 2009), angioimmunoblastic T-cell lymphoma (Xerri *et al*, 2008), (Wilcox *et al*, 2009) and non-Hodgkin lymphoma (Andorsky *et al*, 2011), among others.

Phase II clinical trial combining pidilizumab and rituximab in patients with relapsed follicular lymphoma demonstrated an overall response rate of 66%, with 52% of participants achieving a complete response. No grade 3/4 side effects were observed (Westin *et al*, 2010). Patients with heavily pretreated relapsing or refractory classic Hodgkin lymphoma were recently included as an independent cohort in a dose escalation and cohort expansion phase I study of nivolumab (Armand *et al*, 2014). With an objective response rate as high as 87% (20 out of 23) including 17% complete responses and a PFS rate at 24 weeks of 86%, a phase II trial of nivolumab in this subset of patients is already underway.

Patients with relapsed or refractory classical Hodgkin lymphoma were evaluated as a cohort of the ongoing multicentre, open-label, phase Ib clinical trial of pembrolizumab in haematologic malignancies and patients were treated with single-agent pembrolizumab $10\,mg\,kg^{-1}$ administered intravenously every 2 weeks. Twenty per cent of the 15 evaluable patients had a CR at 12 weeks. Additionally, 33% had partial remission as best overall response, for an overall response rate of 53% (Moskowitz *et al*, 2014).

CONCLUSION

Anti-PD-1/L-1 antibodies are revitalising interest in solid tumour immunotherapy after demonstrating impressive rates of clinical benefit in patients with different neoplasms, some of them classically not considered immunoresponsive. We are starting to understand which patients are more likely to benefit from anti-PD-1/L1-blocking strategies, and the potential for biomarkers associated with response will ultimately lead to improved patient care. Because of the complexity of the tumour environment, the high number of cells and molecules implicated in tumour immune evasion and therefore potential therapeutic targets, further studies might likely uncover additional immunologic checkpoints, which can be targeted alone or in combination with other immunotherapeutic approaches. Such combinations will need to be developed under a strong preclinical rational and taking into consideration the differences in the development of immunotherapeutic agents compared with classic anticancer agents.

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