

# Immune checkpoint blockade: the role of PD-1-PD-L axis in lymphoid malignancies

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**Abstract:** The co-inhibitory receptor programmed cell death (PD)-1, expressed by immune effector cells, is credited with a protective role for normal tissue during immune responses, by limiting the extent of effector activation. Its presently known ligands, programmed death ligands (PD-Ls) 1 and 2, are expressed by a variety of cells including cancer cells, suggesting a role for these molecules as an immune evasion mechanism. Blocking of the PD-1-PD-L signaling axis has recently been shown to be effective and was clinically approved in relapsed/refractory tumors such as malignant melanoma and lung cancer, but also classical Hodgkin's lymphoma. A plethora of trials exploring PD-1 blockade in cancer are ongoing. Here, we review the role of PD-1 signaling in lymphoid malignancies, and the latest results of trials investigating PD-1 or PD-L1 blocking agents in this group of diseases. Early phase studies proved very promising, leading to the clinical approval of a PD-1 blocking agent in Hodgkin's lymphoma, and Phase III clinical studies are either planned or ongoing in most lymphoid malignancies.

**Keywords:** immune checkpoint blockade, programmed cell death 1, b7 antigens, hematological cancer, lymphoma, chronic lymphocytic leukemia

## Background

Regulation of T-cell activation consists of two distinct signals. The primary signal is represented by a specific interaction between the T-cell receptor (TCR) and the antigen bound by the major histocompatibility complex molecule on the surface of the antigen presenting cells (APCs). The second signal is mediated through co-stimulation of lymphocyte receptor CD28 by B7 ligands (CD80, CD86) induced on the APC by pathogens, playing an important role in T-cell activation and tolerance. However, co-inhibitory signaling can limit activation and suppress effector T-cell actions and is as such credited with a protective role, by limiting immune damage to healthy tissue and inducing tolerance. Molecules such as cytotoxic T lymphocyte associated protein 4 (CTLA-4), programmed cell death 1 (PD-1) and its ligands, programmed death-ligand (PD-L) 1 and 2, are members of the B7/CD28 ligand-receptor family and represent the most investigated inhibitory immune checkpoints at present.<sup>1</sup>

The PD-1 (CD279) receptor is a transmembrane protein of the immunoglobulin superfamily and was first identified and characterized in 1992 in mice.<sup>2,3</sup> It is a co-inhibitory receptor found on the surface of T cells, B cells, monocytes, and activated natural killer cells.<sup>4</sup> The receptor interacts with its two ligands, PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273)<sup>5,6</sup> expressed by APCs, PD-L1 being regarded as the main mediator of PD-1 dependent immunosuppression.<sup>7</sup> This ligand is constitutively expressed on T cells, B cells, macrophages, and dendritic cells, as well as nonimmune cells, such as endothelial cells,  $\beta$  pancreatic cells, glial cells, epithelial

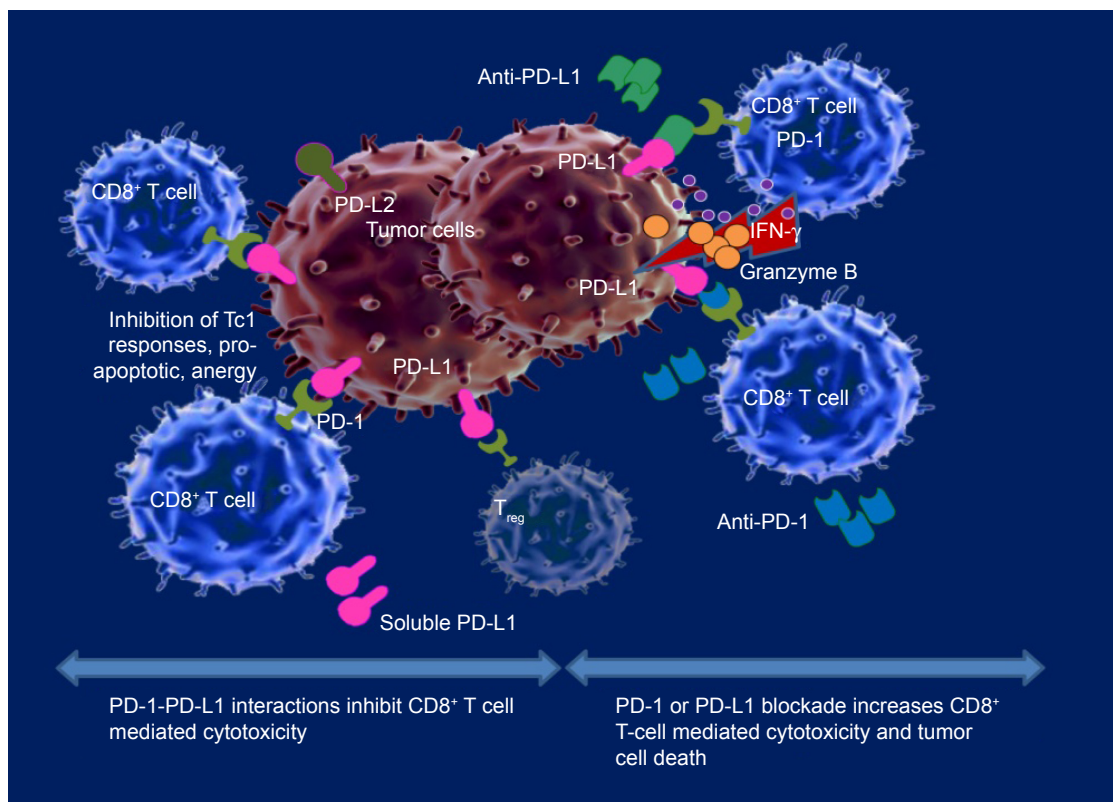
cells, and muscle fibers.<sup>8–10</sup> In contrast to PD-L1, PD-L2 has a more narrow expression profile, restricted to APC and helper T cells, but an affinity approximately two to sixfold higher, hence the possibility of competition between ligands for the binding of the receptor.<sup>5,11,12</sup> Also, the mechanism of action of the two ligands differs: PD-L1 binds to both PD-1 and CD80, whereas PD-L2 interacts directly with PD-1.<sup>6</sup>

The PD-1-PD-L pathway downregulates the immune response to maintain a balance between T cell activation and healthy tissue destruction, thus preserving peripheral tolerance (Figure 1).<sup>13–15</sup> T cell activation is followed by upregulation of PD-1 and production of cytokines, such as interferon (IFN)- $\gamma$  and interleukin (IL)-4. These cytokines upregulate PD-L1 expression through a positive feedback mechanism, having a role in preventing autoimmunity and tissue destruction.<sup>16,17</sup> In case of an inadequate immune response, prolonged antigen stimulation causes PD-1 upregulation and T cell exhaustion. The critical role of downregulation of the immune system through PD-1 stimulation has been demonstrated in a series of studies on chronic viral infections such as HIV, hepatitis B and hepatitis C, whereas CD8<sup>+</sup> T cells have impaired proliferation responses and

cytokine production, and are often described as exhausted T cells.<sup>18–20</sup> In these cases there is a persistent T cell activation with PD-1 upregulation and, consecutively, PD-1-PD-L1 pathway stimulation, resulting in inactive T cells, infection persistence and a minimized immune aggressive effect on healthy tissues.<sup>21</sup>

## Role of PD-1-PD-L pathway in cancer

Involvement of the PD-1-PD-L pathway in cancer has been demonstrated in a broad variety of solid malignancies, such as breast cancer, colon carcinoma, lung cancer, renal cell cancer, melanoma, ovarian cancer, bladder cancer, pancreatic cancer, and various hematologic malignancies.<sup>7,22–26</sup> PD-1 levels are considerably upregulated on tumor-infiltrating lymphocytes (TILs) in comparison to peripheral blood or healthy tissues infiltrating T cells, and consecutively TILs exert an impaired antitumor activity.<sup>5,27–30</sup> Compared to PD-1<sup>−</sup> lymphocytes, PD-1<sup>+</sup> TILs exhibit an “exhausted” phenotype, through decreased TCR signaling, defective calcium flux and diminished cytokine production including IL-2, IFN- $\gamma$ , and TNF $\alpha$ .<sup>28,29,31–34</sup> PD-L1 expression is encountered in a large variety of tumors as well: lung, breast, colon, skin, ovarian,



**Figure 1** PD-1- PD-L1 axis blockade in cancer.

**Notes:** Signaling through PD-1 induces T cell anergy, with the physiological role of protecting from autoimmune damage. This mechanism is exploited by tumor cells expressing PD-I ligands to escape immunity by suppressing host antitumor T cell responses (left). PD-1 or PD-L1 blocking antibodies have the capability to restore cytotoxic T cell functions including IFN- $\gamma$  and perforin production, which can lead to impressive antitumor responses (right).

**Abbreviations:** PD, programmed cell death; PD-L1, programmed cell death receptor ligand-1.

gastric, pancreatic cancers, and different types of hematologic malignancies.<sup>17,35–38</sup> The ligand is upregulated at the surface of cancer cells, intratumoral macrophages and APCs from the surrounding tumor microenvironment. PD-L1 appears to act as an antiapoptotic factor in cancer cells, as its expression is strongly associated with *in vivo* tumorigenesis and invasion, and *in vitro* resistance to T cell mediated lysis.<sup>1,39</sup> The ligand upregulation is triggered by proinflammatory cytokines such as IFN- $\gamma$  produced by lymphocytes present in the tumor microenvironment.<sup>38</sup> Therefore, activation of the PD-1–PD-L1 immune checkpoint pathway in cancer represents an adaptive mechanism of resistance used by cancer cells against TILs, suggesting the presence, yet exhaustion of an antitumor T-cell immune response.

*In vitro* studies have demonstrated that blockade of PD-1 or PD-L1 using monoclonal antibodies restored T cell cytotoxic capacity and IFN- $\gamma$  production (Figure 1).<sup>1,40</sup> Subsequently, clinical studies have confirmed these findings, with PD-1 and PD-L1 blocking antibodies being successful at present and having been recently approved by the US Food and Drug Administration for the treatment of metastatic melanoma, nonsmall cell lung cancer, renal cell and urothelial carcinoma, head and neck cancer, and classical Hodgkin's lymphoma (cHL) (Table 1).

## Potential biomarkers for the efficacy of PD-1–PD-L blockade

PD-L1 and/or PD-1 expression were actively investigated as potential biomarkers to predict the efficacy of PD-1–PD-L1 axis blockade. Initial studies and preclinical data in solid tumors have found a correlation between PD-L1 expression and clinical benefits of PD-1 blockade, suggesting that the ligand might be a promising biomarker, with a better association to the treatment response in comparison with PD-1 expression.<sup>41</sup> A strong correlation between PD-L1<sup>+</sup> expression in malignant cells and the response to PD-1

blockers has been demonstrated in lung cancer,<sup>42</sup> but also in melanoma,<sup>43</sup> breast cancer,<sup>44</sup> hepatocellular carcinoma,<sup>45</sup> and colorectal cancer,<sup>46</sup> whereas in renal cell carcinoma and urothelial carcinoma PD-L1<sup>+</sup> infiltrating cells correlate best with response to anti-PD-L1 antibodies.<sup>47–49</sup>

Some of the difficulties encountered in PD-L1 evaluation were the limited tumoral tissue availability, the tissue heterogeneity, and the markers' dynamic, the expression of which is influenced by infections, malignancies, and treatment. Although early phase studies in advanced solid cancers such as melanoma, lung cancer, colorectal cancer, renal-cell cancer, and prostate cancer demonstrated clinical benefits in PD-L1<sup>+</sup> tumors and none in PD-L1<sup>−</sup> cohorts,<sup>1,7,50</sup> a recent Phase III randomized trial of nivolumab, an anti-PD-1 human IgG4 monoclonal antibody, in melanoma showed improved survival in all subgroups, regardless of the levels of PD-L1 expression, but objective response rates (ORRs) were significantly higher in the PD-L1<sup>+</sup> subgroup (52.7%) than in the PD-L1<sup>−</sup> one (33.1%).<sup>51</sup> Nevertheless, even patients with tumors lacking PD-L1 expression can benefit from anti-PD-1 therapy, probably due to tumor microenvironment responsiveness.<sup>1,49,52</sup> Therefore, a lack of PD-L1 expression is not an appropriate biomarker for patient exclusion, with PD-L1 status being rather appropriate for stratification into groups that would benefit from anti-PD-1 monotherapy and groups that are in need of combination therapy in order to achieve a better response.<sup>52</sup> However, the recent approval by the US Food and Drug Administration (FDA) of anti PD-1 agent pembrolizumab for nonsmall cell lung cancer is conditional on the demonstration of tumor PD-L1 expression by an FDA-approved test.

The differences between data obtained in various clinical trials may be attributed to different cutoff values for PD-L1 expression varying in different trials from as low as 1%<sup>53</sup> to the more frequently used 5%,<sup>54,55</sup> and even as high as 50% of tumor cells.<sup>53</sup> Uniformization and standardization of PD-L1 expression assessment, including the positive cutoff value,

**Table 1** US Food and Drug Administration-approved PD-1 checkpoint blockers

Drug	Activity	Approved for	Observations
Nivolumab	Anti-PD-1 human IgG4 mAb	Metastatic melanoma Classical Hodgkin's lymphoma Nonsmall cell lung cancer Renal cell carcinoma	Single or in combination with ipilimumab After ASCT and brentuximab vedotin failure Progression after platinum and/or other agents After prior anti-angiogenic therapy
Pembrolizumab	Anti-PD-1 humanized IgG1 mAb	Melanoma (unresectable/metastatic) Nonsmall cell lung cancer Head and neck squamous cell carcinoma	Approval restricted to PD-L1 expressing tumors Progression after or on platinum-containing treatment
Atezolizumab	Anti-PD-L1 humanized IgG1 mAb	Metastatic nonsmall cell lung cancer Urothelial cancer	Progression after platinum and/or other agents Metastatic or locally advanced

**Abbreviations:** ASCT, autologous stem cell transplantation; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death receptor ligand 1.

the selective staining of tumor cells or infiltrating immune cells and the types of antibody used, is of major significance for future trials. A sensitivity analysis of 20 trials of PD-1 axis blockers' efficacy according to PD-L1 expression in solid tumors which used thresholds of 1% and 5% ligand expression by immunostaining, underscored the above shortcomings and concluded that a cutoff of 5% should be used for PD-L1 expression assessment.<sup>56</sup>

The mechanism of anti-PD-1 therapy action differs between solid tumors and hematologic malignancies. PD-1 evaluation as a prognostic marker in lymphoid malignancies has yielded variable results. While in Hodgkin's lymphoma, PD-1 expression correlated with overall survival (OS) being a stage-independent negative prognostic factor,<sup>57,58</sup> the same receptor expressed by TILs represents a positive prognostic marker for progression-free survival (PFS) and OS in cases of follicular lymphomas.<sup>59</sup>

Besides surface expression of PD-1 and its ligands, other biomarkers have been evaluated to predict efficacy of the PD-1 signaling blockade. These include the presence of soluble PD-L1 (sPD-L1) in patients' sera,<sup>60,61</sup> the ratio of immune cells subtypes in the tumor microenvironment,<sup>62,63</sup> and immune gene expression signature.<sup>64</sup> Specific biomarkers of PD-1 axis blockade investigated in lymphoproliferative disease will be discussed in the respective sections below.

## PD-1-PD-L1 pathway blockade in hematological malignancies

Hematological cancers have, too, developed diverse strategies of evading the immune system. Since the impressive effect of PD-1 blockade has been proven, PD-1 or PD-L1 targeted antibodies are being investigated for the treatment of various types of hematological malignancies. The use of immune checkpoint blockade in these pathologies is limited, but has shown clinical benefit in relapsed or refractory disease settings.<sup>3</sup> Markers of the PD-1 pathway, evaluated by immunohistochemistry or flow cytometry, have been confirmed in hematologic diseases such as multiple myeloma (MM), acute myeloid leukemia, and Hodgkin and non-Hodgkin lymphomas (NHL).<sup>57,65</sup> Of the NHLs, PD-1 and ligands expression has been confirmed in chronic lymphocytic leukemia (CLL),<sup>66</sup> follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBL), anaplastic large-cell lymphoma, and angioimmunoblastic T-cell lymphoma (AITL).<sup>57,67-69</sup>

The timing of PD-1 blockade initiation is crucial and there are several temporal aspects under consideration in the optimization of treatment outcome. First, initiation of anti-PD-1

antibody treatment prior to chemotherapy may enhance antitumor immune responses offering a better support for subsequent treatment. Second, use of immune checkpoint blockade concomitantly with classical chemotherapy could enhance the antitumor response by creating a tumor antigen-rich environment consecutive to cell lysis, which can further stimulate the immune system. Finally, a third option would be the administration of PD-1 blockers after the cytotoxic treatment, boosting the antitumor response during a period of immune reconstitution subsequent to chemotherapy-induced myelosuppression.<sup>57</sup> Also, chemotherapy induces PD-1 expression on immune cells, favoring the immune checkpoint blockade being administered postcytotoxic treatment.<sup>21,70,71</sup> Based on this reasoning, anti-PD-1 therapy could be applied either before autologous/allogeneic stem cells transplantation (ASCT), or to target residual disease after transplantation, when PD-1 pathways may serve as a tumor survival mechanism.<sup>52,72,73</sup>

The response to PD-1 blockade varies significantly between different types of lymphoma, due to the diverse mechanisms responsible for the expression of co-inhibitory molecules, and no definitive correlations have been yet established. PD-L1 is an inducible molecule that can be stimulated by viral infections, TILs, or genetic changes within the tumor.<sup>69,74</sup> Also, high levels of sPD-L1 may be secreted by tumor-infiltrating cells following proinflammatory cytokine stimulation.<sup>36</sup>

While in solid tumors PD-L1 is highly expressed on cancer cells but minimally expressed in the surrounding normal tissue,<sup>22</sup> in up to 73% of T-cell NHL subtypes PD-L1 expression is more prevalent on tumor-infiltrating cells as compared to malignant cells, contributing to immune suppression.<sup>75,76</sup>

DLBCL cells employ multiple mechanisms for the upregulation of PD-1 and its ligands, occasionally present on the same tumor cell, in contrast to FL, where PD-1 is highly expressed in the microenvironment, highlighting different immune evasion strategies.<sup>62,68,77,78</sup>

Strong PD-L1 expression in DLBCL tumor cells is significantly associated with Epstein-Barr virus (EBV) infection, and is higher in activated B cell-like than in germinal center B cell-like phenotypes. The levels of PD-1<sup>+</sup> TIL correlated positively with the level of PD-L1 expression in tumor cells or macrophages.<sup>79</sup>

Similar to HL, where EBV latent membrane protein 1 (LMP-1) increases PD-L1 promoter activity, PD-L1 expression in DLBCL may be upregulated by EBV infection.<sup>80,81</sup> Similar to genetic aberrations encountered in HL, several



gene expression profiling studies demonstrated the presence of gains/amplifications of a region of chromosome 9p24 in ~70% of PMBL cases, leading to a high expression of PD-L1 and 2, which distinguishes PMBL from other types of DLBCL and could serve as a molecular diagnostic tool.<sup>82–84</sup>

Primary central nervous system lymphomas (PCNSLs) and primary testicular lymphomas have also been shown to exhibit 9p24.1 copy gain and chromosomal translocation of PD-L1/PD-L2, as well as EBV-mediated upregulation of the ligands in PCNSL.<sup>85</sup>

An association between viral infections and PD-L1 expression was also observed in other lymphoid malignancies. Studies on EBV-positive natural killer/T-cell lymphoma found a high expression of PD-L1 in lymphoma cells, upregulated by LMP1 through the MAPK/NF- $\kappa$ B pathway. High PD-L1 expression (>38%) and serum sPD-L1 levels  $\geq 3.4$  ng/mL were interpreted as independent prognostic factors for lower complete remission (CR) rates, PFS, and OS.<sup>86</sup> Also, in extranodal NK/T-cell lymphoma (ENKTL) treated with asparaginase, high posttreatment sPD-L1 level (>1.12 ng/mL) was demonstrated to be a predictive biomarker for early relapse and poor prognosis and also a marker of minimal residual disease.<sup>87</sup> However, results from another study show that high PD-L1 expression in advanced stages of EBV<sup>+</sup> ENKTL correlates with improves OS,<sup>88</sup> further studies being warranted to establish the prognostic value of PD-L1 expression in these cases. In adult T-cell leukemia/lymphoma (ATLL), HTLV-1 bZIP factor expressed by HTLV-1 infected cells upregulates PD-1 expression on both neoplastic and normal CD4<sup>+</sup> T cells, but impedes its suppressive signals by inhibiting co-localization of PD-1 and tyrosine phosphatase (SHP-2), favoring the proliferation of infected cells and immune suppression.<sup>89,90</sup> Both asymptomatic HTLV-1 carriers and ATLL patients express high PD-1 levels on HTLV-1-specific cytotoxic T cells, with elevated levels in patients with EBV and CMV co-infection. PD-L1 expression was only identified in ATLL cells of the patients and administration of an anti-PD-L1 or anti-PD-1 antibody stimulated HTLV<sup>+</sup> CD8<sup>+</sup> T cell immune response.<sup>91,92</sup>

In the next sections, we review results of PD-1 blockade studies in lymphoproliferative diseases, the most relevant clinical trial efficacy reports being summarized in Table 2.

## Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is an ideal candidate for anti-PD-1 therapy, because of its particular histological structure, which involves a rather small number of primary tumor-associated CD-30<sup>+</sup> Reed Sternberg or Hodgkin cells surrounded by a

granuloma-like, immune cell-rich environment. A viral or genetic-induced PD-L1 overexpression by Reed Sternberg malignant cells was also described.<sup>93</sup> Thus, not surprisingly, of the several clinical studies evaluating PD-1 blockade efficiency in hematologic malignancies, the most promising results have been recorded for patients with cHL. Consecutively, cHL is the first hematologic malignancy in which an anti-PD-1 agent, nivolumab, has been approved, in early 2016, as salvage therapy after prior ASCT and brentuximab. The breakthrough therapy designation by the FDA is based on results of a Phase I (CheckMate-039)<sup>93</sup> and a Phase II (Checkmate-205)<sup>94,95</sup> trial (Table 2).

The PD-L1 gene has been identified in HL and is located on the short arm of chromosome 9p24. Amplification of genetic material in the 9p24 region is associated with PD-1 ligand overexpression in nodular sclerosis HL and also PMBL: mostly PD-L1 in HL and PD-L2 in PMBL. Amplification of this region also results in amplification of JAK2, which through JAK2-STAT signaling further stimulates PD-1 ligand overexpression.<sup>66,83</sup> Immune cells surrounding Reed Sternberg cells include PD-1<sup>+</sup> T-cells, whose function and IFN- $\gamma$  production can be stimulated by immune checkpoint blockade.<sup>38,65</sup> Epstein–Barr infection, commonly associated with HL, is another mechanism involved in PD-L1 upregulation,<sup>80</sup> viral infections being known as able to exploit the PD-1–PD-L pathway in order to induce immune tolerance.<sup>40,52</sup>

## Chronic lymphocytic leukemia

CLL is the most frequent B cell malignancy, characterized by an increased proliferation and accumulation of monoclonal CD5<sup>+</sup> CD19<sup>+</sup> B cells in the bone marrow, lymphoid organs, and peripheral blood, promoting a tumor microenvironment which dampens the immune response and favors malignant cell proliferation and treatment resistance.<sup>96,97</sup> Recent studies described a functional impairment in the T-cell compartment (both CD4<sup>+</sup> and CD8<sup>+</sup>) reflected by alterations of their number, function and memory, as a consequence of interaction with leukemic cells.<sup>37,98</sup> T-cells are found in a state of chronic activation and have the tendency to accumulate, presenting an inversion of the normal CD4:CD8 ratio, higher levels of CD8<sup>+</sup> T cells being associated with a more aggressive disease.<sup>99</sup>

The PD-1–PD-L1 axis has been shown to be involved in CLL pathogenesis. Immunohistochemistry and immunofluorescence assays of PD-1 and PD-L1 expression in lymph nodes of CLL patients demonstrated the presence of PD1<sup>+</sup> CD4<sup>+</sup> T cells and PD-L1<sup>+</sup> CD23<sup>+</sup> B cells.<sup>37</sup> Both T cells

Table 2 Selected clinical trial results of PD-1/PD-L1 checkpoint blockade efficacy in lymphoid malignancy

Interventional clinical trial number	Type of study	Participants	Description: dose and trial duration	Posted/published results	Comments/limits
<b>Hodgkin's lymphoma</b>					
NCT01592370 CheckMate-039	Interventional Phase I dose-escalation and expansion, nivolumab Ansell et al <sup>93</sup>	23 patients with R/R HL, 87% had >2 previous regimens, 78% had ASCT, 78% had BV, Median age 35 years	Nivolumab 3 mg/kg at week 1, week 4, and then every 2 weeks until progressive disease, CR, toxicity or for a maximum of 2 years. Median duration of follow-up was 40 weeks	ORR: 20 (87%) CR: 4 (17%) PR: 16 (70%) SD: 3 (13%)	Acceptable safety profile Good overall response Majority of adverse events grade I or 2
	Extended follow-up, nivolumab Ansell et al <sup>127</sup>	Same as above	Same dose as above; median duration of follow-up was 86 weeks	20 responders, 10 durable responses Responses occurred within 16 weeks of initiation in 15 of 20 patients 5 patients with early responses proceeded to SCT (4 allo-, 1 ASCT) Responses lasted $\geq 1$ year in 7 of 10 patients who did not undergo SCT	Positive study for extended response
NCT02181738 CheckMate-205	Noncomparative, multi-cohort, single arm, open-label, Phase II study of nivolumab in cHL subjects. Report on cohort B. Timmerman et al <sup>95</sup>	80 patients in R/R previously treated with BV after ASCT failure Median age 37 years (18–72) Median prior therapies: 4	Nivolumab 3 mg/kg every 2 weeks Median follow-up 15.4 months 43 (54%) still on therapy at cutoff	ORR: 68% CR: 8% PR: 60% Median duration of CR: NR Median duration PR: 13.1 months Median PFS: 14.8 months 12 month PFS: 54.6% 12 month OS: 94.9% Investigator review: ORR: 65%, CR: 19% Blinded independent central review: ORR 58%, CR 19%, PR 39%, SD 23% 6 months OS: 100% 12 month OS: 87% Investigator review: ORR: 66.7%, 65.4% and 69.3% CR: 29%, 24.7%, 21.7% Blinded independent central review: ORR: 72.5%, 65.4%, 66.7% CR: 21.7%, 22.2%, 21.7% respectively, for the 3 cohorts	Positive study Preliminary results of this study together with Checkmate-039 results led to FDA approval of nivolumab in May 2016 for R/R cHL after ASCT and brentuximab
NCT01953692 Keynote-013	Phase Ib study of pembrolizumab in cHL patients after BV failure: long-term efficacy report Armand et al <sup>128</sup>	31 patients relapsed after or ineligible for ASCT and R/R after BV, median prior therapy lines 5	Pembrolizumab 10 mg/kg every 2 weeks until progressive disease, toxicity or up to 2 years Median follow-up 24.9 months	Investigator review: ORR: 65%, CR: 19% Blinded independent central review: ORR 58%, CR 19%, PR 39%, SD 23% 6 months OS: 100% 12 month OS: 87% Investigator review: ORR: 66.7%, 65.4% and 69.3% CR: 29%, 24.7%, 21.7% Blinded independent central review: ORR: 72.5%, 65.4%, 66.7% CR: 21.7%, 22.2%, 21.7% respectively, for the 3 cohorts	Positive study, median survival NR at >2 years
NCT02453594 Keynote-087	Phase II study of pembrolizumab in R/R cHL and BV (69), ineligible for ASCT and primary end point analysis Moskowitz et al <sup>129</sup>	210 patients, 3 cohorts: prior ASCT and BV (69), ineligible for ASCT and BV failure (81), and R/R to prior ASCT and no BV (60)	Pembrolizumab 200 mg intravenous every 3 weeks	Investigator review: ORR: 66.7%, 65.4% and 69.3% CR: 29%, 24.7%, 21.7% Blinded independent central review: ORR: 72.5%, 65.4%, 66.7% CR: 21.7%, 22.2%, 21.7% respectively, for the 3 cohorts	Positive study
<b>Chronic lymphocytic leukemia</b>					
NCT02332980 MCI485	Phase II study of pembrolizumab alone or with idelalisib or ibrutinib in R/R CLL and RS. Ding et al <sup>130</sup>	25 patients: 16 with CLL and 9 with RS. Enrolled in the CLL arm of the study. Median age 69 years (46–81)	Pembrolizumab 200 mg intravenous q 3 weeks	RS: CR: 1 (1%) PR: 3 (33%) SD: 3 (33%) Progressive disease: 2 (22%)	Single agent pembrolizumab seems to have better activity in RS than in CLL, results being rather negative for the latter

NCT02420912	Phase II study of nivolumab plus ibrutinib in CLL and RS. Jain et al <sup>31</sup>	12 (48%) with del (17p)/monosomy 17/TP53 mutation. Median number of prior therapies: 4 (1–10) Cohort 1: R/R CLL (5 patients) or RS (4 patients) Cohort 2: CLL in PR after min. 9 months of ibrutinib, N=3 pts Median age 63 years (42–78) Median number of prior therapies: 1 (1–3)	Median number of doses: 3 (1–21)  Nivolumab 3 mg/kg IV every 2 weeks, ibrutinib 420 mg/day For cohort 1: a first course of single-agent nivolumab followed by adjunction of ibrutinib	CLL: No CR/PR 6-month OS: 73% for RS vs 59% for CLL  Cohort 1, CLL PR: 3 pts No response and withdrawal: 1 patient Non-assessable: 1 patient Cohort 1, RS: 2 patients with PR, 1 with PD, 1 non-assessable Cohort 2: no CR, all 3 patients showed decreased marrow infiltration	Early results are promising, study is ongoing
<b>B-NHL</b>					
NCT01592370 CheckMate-039	Phase Ib study of nivolumab in R/R hematologic malignancy Lesokhin et al <sup>25</sup>	105 total 31 patients with R/R B-NHL (of which 11 DLBCL, 10 FL, 10 other) Median age 65 years (23–74)	Nivolumab 1 and 3 mg/kg at week 1, week 4, and then every 2 weeks until PD, CR, toxicity or for a maximum of 2 years	DLBCL: CR: 2 (18%), PR: 2 (18%), SD: 3 (27%), median PFS: 7 weeks FL: 4 (40%), CR: 1 (10%), PR: 3 (30%), SD: 6 (60%), median PFS: NR Other: CR: 0, PR: 0, SD: 7 (70%), median PFS: 11 weeks (3–39) CR: 2 PR: 5 SD: 6 Median follow-up: 11.3 months (24–27.4), median duration of response NR	Acceptable safety profile and positive objective response rate leading to Phase II studies in DLBCL and FL  Manageable safety profile, promising antitumor activity
NCT01953692 Keynote-013	Phase Ib study of pembrolizumab in R/R PMBL Zinzani et al <sup>32</sup>	19 patients with PMBL Median age 30.5 years (22–62)	First 11 patients: pembrolizumab 10 mg/kg q 2 w (1 not treated – early PD) Subsequent patients: pembrolizumab 200 mg q 3 weeks		
<b>T-NHL</b>					
NCT01592370 CheckMate-039	Phase Ib study of nivolumab in R/R hematologic malignancy Lesokhin et al <sup>25</sup>	105 total of which 23 T-NHL: 13 MF, 5 PTCL, 5 other T-NHL Median age 61 years (30–81) 2–6 prior systemic therapies	Nivolumab 1 and 3 mg/kg at week 1, week 4, and then every 2 weeks until PD, CR, toxicity or for a maximum of 2 years	All T-NHL: CR: 0, PR: 4 (17%), SD: 10 (43%), median PFS: 10 weeks MF: CR: 0, PR: 2 (15%), SD: 9 (69%) Median PFS: 10 weeks PTCL: CR: 0, PR: 2 (40%), SD: 0, median PFS: 14 weeks CR: 2 PR: 5 SD: 6 Median follow-up: 11.3 months (24–27.4), median duration of response: NR	Ongoing response in the two MF responders at 24 and 50 weeks, and for one patient with PTCL at 78 weeks  Manageable safety profile, promising antitumor activity
NCT01953692 Keynote-013	Phase Ib study of pembrolizumab in R/R PMBL Zinzani et al <sup>32</sup>	19 patients with PMBL Median age 30.5 years (22–62)	First 11 patients: pembrolizumab 10 mg/kg q 2 w (1 not treated – early progressive disease) Subsequent patients: pembrolizumab 200 mg q 3 w		
<b>Multiple myeloma</b>					
NCT01592370 CheckMate-039	Interventional Phase I dose-escalation and expansion of nivolumab in R/R lymphoid malignancies Lesokhin et al <sup>25</sup>	81 patients with R/R lymphoid malignancies including 27 patients with MM Median age of 63 years (range, 32–81 years)	Dose escalation design (1 mg/kg and 3 mg/kg) of nivolumab administered every 2 weeks for up to 2 years	CR: 1 (4%) Median PFS: 10 weeks (5–15)	Negative study for MM patients

(Continued)

Table 2 (Continued)

Interventional clinical trial number	Type of study	Participants	Description: dose and trial duration	Posted/published results	Comments/limits
NCT02289222	Phase II study of pembrolizumab with pomalidomide and dexamethasone in R/R MM Badros et al <sup>133</sup>	48 patients with MM Median age: 64 years (35–82) Median previous therapies: 3 (2–6)	Pembrolizumab 200 mg q 2 w (first 6 patients: 200 mg q 4 w) plus pomalidomide 4 mg q d 21 days plus dexamethasone 40 mg q w	Stringent CR: 4 Near CR: 3 VGPR: 6 PR: 14 MR: 7 SD: 9 Median duration of response $\geq$ VGPR: 10.7 months Median follow-up: 10 months (2–18) VGPR: 4 PR: 9 Median follow-up: 287 days (48–476)	Acceptable safety profile, promising therapeutic activity
NCT02036502 Keynote-023	Phase I study of pembrolizumab with lenalidomide and dexamethasone in R/R MM San Miguel et al <sup>134</sup>	34 patients; data available for 17 patients Median age 60 years (46–76) 53% had $\geq 3$ previous therapies	4 patients: pembrolizumab 2 mg/kg q 2 w, lenalidomide 10 mg q d 13 patients: pembrolizumab 2 mg/kg or 200 mg and lenalidomide 25 mg All patients: dexamethasone 40 mg q w	Preliminary results positive for safety and anti-myeloma activity. An international Phase III trial, KEYNOTE-183 (NCT02576977), is currently ongoing	

**Abbreviations:** ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; CLL, chronic lymphocytic leukemia; cHL, classical Hodgkin's lymphoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FDA, US Food and Drug Administration; HL, Hodgkin's lymphoma; MM, multiple myeloma; MR, minimal response; NHL, non-Hodgkin's lymphoma; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; PTCL, peripheral T-cell lymphoma; PMBL, primary mediastinal large B-cell lymphoma; PD-1, programmed cell death receptor 1; PD-L, programmed cell death receptor ligand; PFS, progression-free survival; R/R, relapsed/refractory; RS, Richter syndrome; SD, stable disease; SCT, stem cell transplantation; VGPR, very good partial response.

and leukemic cells are present in lymph nodes proliferation centers, suggesting their probable interaction and involvement in CLL pathogenesis.

A study on the effects of early in vivo PD-L1 blockade in a mouse model of CLL showed that administration of anti-PD-L1 antibodies prevented disease progression. Decreased spleen sizes were observed, as well as changes in the tumor load and peripheral blood lymphocytosis. PD-L1 blockade prevented CD8:CD4 ratio inversion, T cell exhaustion, and determined increased CD8 cytotoxicity, growth fraction, in vivo proliferation, and CD8 synapse formation.<sup>100–102</sup>

PD-1 expression is found on CD4<sup>+</sup> and CD8<sup>+</sup> T cells, their proliferation being associated with a negative prognosis,<sup>99</sup> while PD-L1 expression on leukemic cells and mononuclear cells in peripheral blood and bone marrow is higher in CLL patients than in healthy controls.<sup>66,103</sup> Apparently, ligand expression does not correlate with age, sex, LDH levels, white blood cell count or disease stage.<sup>66</sup> However, PD-L1 significantly correlates with PD-1, TIL number, and IFN- $\gamma$  levels, PD-1–PD-L1 interaction suppressing intratumoral cytokine production, and ligand blockade stimulating IFN- $\gamma$  secretion through a negative feedback mechanism.<sup>66,76</sup>

Rusak et al reported that patients with advanced stage CLL have a considerably increased number of PD1<sup>+</sup> CD4<sup>+</sup> T cells in the peripheral blood compared to patients with incipient stages of the disease.<sup>104</sup> Also, patients with lower levels of these lymphocytes achieved CR more frequently through PD-1 blockade, suggesting that the number of PD1<sup>+</sup> CD4<sup>+</sup> T cells correlates with the response obtained with this immunotherapy approach. These findings suggest that quantitative flow cytometric evaluation of PD1<sup>+</sup> CD4<sup>+</sup> T cells could be used for prognostic purposes in newly diagnosed patients.<sup>104</sup>

## Non-Hodgkin lymphoma

PD-1-PD-L blockade is under investigation in various types of NHL, based on evidence of frequent expression of PD-1, PD-L1, and PD-L2 in lymphoid malignancies. Cancer cells drive changes in the host immune response to generate unique microenvironments that promote cancer cell growth. The PD-1-PD-L1 interaction represents an important cause of lymphoma induced T-cell defects, causing changes in T-cell subsets, their effector function, expression of surface molecules, and gene expression profiles. Studies on FL and DLBCL found overexpression of 25 immune escape genes including the ones involved in PD-1–PD-L and CTLA-4 inhibitory axis, the LAG3 and TIM3/galectin T-cell exhaustion axis.<sup>68</sup> Expression of these genes and proteins is considerably higher in DLBCL than in FL. Detectable circulating soluble PD-L1 was reported in DLBCL, and was associated with



a poor prognosis.<sup>105</sup> In a Phase I study of the anti-PD-1 nivolumab in patients with relapsed or refractory T and B-cell lymphomas ORR were 40% in patients with FL, 36% in DLBCL, 15% in mycosis fungoides (MF) and 40% in peripheral T-cell lymphoma (PTCL). In the same study it was discovered that malignant cells from MF expressed high levels of PD-L2 and fluorescence in situ hybridization assays revealed chromosomal rearrangements (disomy 9p, polysomy 9p, and PD-L2 translocation), responsible for the ligand overexpression.<sup>25</sup> Results of clinical trials of PD-1 axis blockade in NHL are summarized in Table 2.

## Diffuse large B-cell lymphoma

PD-L1 is highly expressed by DLBCL (>60% of cases), as compared to other solid tumors, such as melanoma (30%) or nonsmall cell lung cancer (25%–36%).<sup>68</sup> PD-L1 expression by lymphoma cells is considered an independent factor for the OS, being associated with a poor prognosis. The number of PD-1<sup>+</sup> TILs is associated with PD-L1<sup>+</sup> lymphoma cells and PD-L1<sup>+</sup> stromal cells, suggesting a role for the PD-1–PD-L1 pathway in the tumor microenvironment.<sup>78</sup>

Pidilizumab, a humanized IgG1 monoclonal antibody, was initially developed as an anti-PD-1 antibody and was the first one to be evaluated in lymphoid malignancies. Phases I and II studies in DLBCL and FL showed promising results, prompting the development of further anti-PD-1 antibodies.<sup>100</sup> A multicenter Phase II clinical trial where pidilizumab was administered to patients with relapsed or refractory DLBCL after ASCT reported a 16 month PFS of 72%. The reported overall response rate among patients with measurable disease after ASCT was 51%, including 34% CRs and 17% partial remissions.<sup>73</sup> The PFS after posttransplant pidilizumab administration of 72% compares favorably to the PFS of 52% obtained after ASCT alone, in a cohort of autografted patients with chemosensitive DLBCL.<sup>52,73</sup> Interestingly, by the end of 2015, the manufacturer of pidilizumab announced that the drug was no longer to be regarded as a PD-1 inhibitor. However, trials of pidilizumab in lymphoma yielded encouraging results and will go on, despite the mechanisms of the immune regulatory action of the drug not being precisely known.

Quan et al evaluated the efficacy of PD-1 blockade in Epstein–Barr virus (EBV)-associated DLBCL (EBV<sup>+</sup> DLBCL), an aggressive lymphoma, highly resistant to current treatments and a potential target for immunotherapy. The number of effector/memory PD-1<sup>+</sup> T cells is more elevated in the lymph nodes than in the peripheral blood, suggesting the immune suppressive effect of the tumor microenvironment in DLBCL. CD8<sup>+</sup> PD-1<sup>+</sup> and CD4<sup>+</sup> PD-1<sup>+</sup> T cells also

expressed CTLA-4, marker of T cell exhaustion. Lymphoma cells upregulate PD-1 expression on T cells and inhibit their proliferation and secretion of IL-2, IFN- $\gamma$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-10. PD-1 blockade reversed these effects, increasing T-cell proliferation and cytokine secretion. Also, it was shown in vitro that PD-1 blockade is more potent in EBV<sup>+</sup> than in EBV<sup>−</sup> DLBCL.<sup>81</sup> A French multicenter randomized trial in DLBCL patients receiving standard chemoimmunotherapy versus high-dose therapy revealed that levels of sPD-L1, with a cutoff of 1.52 ng/mL, had negative predictive value for OS, elevated levels being significantly correlated with a poorer prognosis in the standard chemoimmunotherapy arm, and suggesting a potential benefit of PD-1 axis blocking therapy in these patients.<sup>105</sup>

## Follicular lymphoma

FL is a hematologic malignancy characterized by an indolent heterogeneous evolution, relapses alternating with remissions and a 7–10 years median survival. In 10%–15% of the cases it behaves aggressively or transforms to DLBCL, leading to poor treatment response and short survival.<sup>59</sup> Gene expression profile and immunophenotyping of nonmalignant cells from FL have highlighted the involvement of the microenvironment in the clinical evolution and treatment response.<sup>59</sup> Unlike CLL, where T cell defects also appear in the peripheral blood, in FL T cells are impaired only in the lymph nodes.

There is controversial evidence regarding PD-1 expression and its prognostic value in FL. Muenst et al showed that grade 1 FL has a higher number of PD-1<sup>+</sup> TILs than secondary DLBCL derived from FL. Also, PD-1<sup>+</sup> TILs may influence tumor behavior in FL and secondary DLBCL arising from FL, being associated with improved disease specific survival in these entities.<sup>106</sup>

Carreras et al concluded that increased numbers of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes are favorable prognostic markers. PD-1<sup>+</sup> cells and T<sub>regs</sub> are localized in the tumoral follicular compartment, playing a role in inhibition of T cell activation and immunomodulation of the microenvironment. PD-1<sup>+</sup> TILs are an independent prognostic marker of survival in patients with FL and their number decreases with transformation to DLBCL.<sup>59</sup> In a study on 70 FL patients selected for either very good or very poor outcome, CD4<sup>+</sup> follicular cells were associated with poor outcome, whereas PD-1<sup>+</sup> follicular cells and CD8<sup>+</sup> interfollicular cells were associated with a good outcome. As far as tumor-microenvironment cell ratios were concerned, high CD4/CD8 and CD4 follicular/interfollicular ratios appeared to be markers of poor outcome.<sup>62</sup> A study conducted by Myklebust et al showed that PD-L1 expression is present in histocytes,

in T cell-rich areas between the follicles, playing an inhibitory role in T-cell activation.<sup>77</sup> High numbers of tissue-infiltrating macrophages were associated with unfavorable evolution and TILs from FL have an impaired activity, probably mediated by the malignant B cells of the lymphoma. Follicular localization of T<sub>regs</sub> correlated with poor clinical outcome and increased risk of transformation.<sup>77</sup>

FL microenvironment includes a variety of T-cell subsets that express PD-1: antitumor effector T cells (helper CD4<sup>+</sup> T and cytotoxic CD8<sup>+</sup> T cells), protumoral follicular helper T cells (T<sub>FH</sub>) and follicular regulatory T cells, with a role in suppressing lymphoma cells and T<sub>FH</sub>.<sup>107</sup> T<sub>FH</sub> are localized in intrafollicular regions and highly express PD-1, whereas exhausted T cells reside in interfollicular areas and express low levels of PD-1.<sup>108</sup> Therefore, inconsistency regarding the prognostic value of PD-1<sup>+</sup> T cells in FL is probably caused by the multiple types of cells expressing PD-1 receptor and by the effects of the PD-1 blockade on every subset.<sup>107</sup> Patients with higher numbers of PD-1<sup>+</sup> effector T cells may have a positive response at anti-PD-1 antibody administration, whereas patients with higher numbers of PD-1<sup>+</sup> T<sub>FH</sub> may have no response or develop disease progression after PD-1 blockade.<sup>109</sup>

Reported clinical trial results showed promising results for nivolumab in R/R FL, albeit not as good as in cHL (Table 2).

## Cutaneous T-cell lymphoma (CTCL)/mycosis fungoides

PD-1 is frequently expressed in the early stages of CTCL, where >25% of atypical lymphocytes express the receptor. PD-1 expression diminishes in the tumor stage of the lymphoma and in cases of large cell transformation. PD-L1 is expressed by the majority of atypical lymphocytes during all stages of lymphoma evolution and increases with disease progression and large cell transformation.<sup>110</sup> Therefore, administration of anti-PD-1 antibodies may restore the immune function of the lymphocytes and could be used in the early stages of CTCL, when PD-1 expression is the most pronounced. In more advanced stages when PD-L1 is highly expressed and the lymphoma is more aggressive, administration of anti-PD-L1 antibodies should improve the antitumor immunity.<sup>110</sup>

## Peripheral T-cell lymphoma

PTCLs are malignancies derived from postthymic T-cells. The most common types include AITL and PTCL, not otherwise specified (NOS). Both AITL and PTCL are

characterized by atypical lymphocytes in the paracortical zones of the lymph nodes. Results from a study on PD-1 expression in PTCL demonstrated that extrafollicular expansion of PD-1<sup>+</sup> T cells was encountered in 93% of the AITL cases and 62% of PTCL.<sup>111</sup>

In another study all cases of AITL showed reactivity for PD-1, which is expressed on the cell surface and in the cytoplasm of neoplastic CD4<sup>+</sup> T cells. In reactive lymph nodes, PD-1 expression is mainly localized in the germinal centers, similar to another marker encountered in AITL, CXCL13, a chemokine that distinguishes AITL from PTCL.<sup>67</sup> However, studies showed that PD-1 can serve as a sensible, but not specific marker for the diagnosis of AITL and PTCL-NOS, because a similar abnormal PD-1 staining pattern is observed in nonmalignant diseases such as viral lymphadenitis, highlighting the importance of differential diagnosis in these situations.<sup>111,112</sup>

## Multiple myeloma

MM, an incurable B cell malignancy, is a monoclonal gammopathy characterized by neoplastic proliferation of plasma cells and their accumulation in the bone marrow, causing bone marrow failure, anemia, and osteolytic bone lesions with secondary hypercalcemia. Excessive production of monoclonal protein leads to predisposition to infection and systemic amyloidosis with organ failure (renal, heart, liver, and nervous system).<sup>113</sup> The disease mainly affects the elderly and has a median survival of 4–5 years.<sup>114</sup>

CD138<sup>+</sup> malignant plasma cells and tumor microenvironment cells such as myeloid-derived suppressor cells have an increased expression of PD-L1 compared with normal plasma cells, in which expression of this ligand is insignificant.<sup>115–118</sup> PD-L1<sup>+</sup> plasma cells levels do not correlate with tumor burden, suggesting that the ligand expression is also influenced by factors from the microenvironment. Indeed, populations of dendritic cells accumulate in the bone marrow, express PD-L1 and affect T cell antitumor activity.<sup>119</sup> Stromal cells upregulate PD-L1 levels on myeloma cells, stimulate their proliferation, and dampen the response to chemotherapy, accelerated disease progression being observed in patients with high PD-L1 expression.<sup>114,120</sup>

Myeloma cells accumulate and exert their action in the bone marrow. Their local immunosuppressive effect leads to the presence of a PD-1<sup>+</sup> T cell population with higher dysfunction compared to circulating T cells, as shown in preclinical studies.<sup>23,116,121</sup> PD-1 expression is also elevated on natural killer cells from myeloma patients compared to healthy controls.<sup>122</sup> Direct interaction between the ligand

present on myeloma cells and the receptor expressed by T and natural killer cells inhibits the antitumor immune response and contributes to chemotherapy resistance, while administration of an anti-PD-1 antibody stimulates lymphocyte cytolytic activity against malignant cells and reduces the tumor growth induced by stromal cells.<sup>122–124</sup>

In myeloma patients' serum, high concentrations of soluble PD-L1 were identified and this fraction might also interact with PD-1, contributing to the immune suppression. Correlations between soluble PD-L1, disease aggressiveness, and poorer responses to treatment have been established. A value over 2.78 ng/mL was proposed as an independent prognosis factor for a shorter PFS.<sup>123</sup>

Administration of anti-PD-L1 antibodies after chemotherapy overthrows tumor-induced immunosuppression and restores lymphocyte production of IFN- $\gamma$  consecutive to tumor antigen stimulation. When both CD4<sup>+</sup> and CD8<sup>+</sup> T cells were reactivated, PD-L1 blockade determined successful myeloma eradication in preclinical studies.<sup>125,126</sup>

## Conclusion

Like with other cancers, immune checkpoint blockade inhibitors are a promising immunotherapeutic option in hematologic malignancies, and PD-1–PD-L1 axis blockers are the most investigated candidates to date. While there are over 600 ongoing clinical trials of PD-1–PD-L axis blockade in oncology, only a small proportion of these are investigating hematologic cancers. Nevertheless, results in hematologic malignancies are extremely promising, and the US FDA granted accelerated approval for nivolumab in cHL in 2016. Fuelled by these results, the number of clinical trials is increasing at a high rate, and many drugs in this class are currently under development. With more early trial results published at this high rate, we expect that immune checkpoint blockade will soon become an integral and well represented target, and feature as part of the management of hematologic malignancy.

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## Disclosure

The authors report no conflicts of interest in this work.

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