Review Article

Stem Cell INVESTIGATION

Immune checkpoint blockade for hematologic malignancies: a review

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Abstract: Immune checkpoint blockade has revolutionized the treatment of cancer, with impressive responses seen in a broad variety of tumor types. Blockade of immune checkpoints and immune signaling antibodies has shown promise in multiple types of hematologic malignancies (HMs), with dramatic single agent responses for pembrolizumab and nivolumab in Hodgkin lymphoma (HL). In this review, we outline the current state of immune checkpoint blockade drug development in HMs, and discuss mechanisms of activity and resistance, and highlight potential targets in the immune tumor microenvironment (TME). Blockade of T-cell checkpoint molecules PD-1/PD-L1 and CTLA-4 are the most clinically mature of the immune checkpoint strategies. Novel and upcoming strategies for immune checkpoint blockade drug development in HMs using innovative combinations to modulate immunologic targets shows significant promise as a way to expand the number of patients with blood cancers who could benefit from immunotherapy.

Keywords: Immunotherapy; multiple myeloma (MM); leukemia; lymphoma; tumor microenvironment (TME)

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Introduction

Immune evasion is a hallmark of cancer (1). This process can be reversed via drugs that block immune checkpoints and bolster endogenous antitumor immune responses as evidenced by the success of CTLA-4 and PD-1 pathway blocking antibodies in melanoma, lung cancer, renal cell carcinoma, and other solid tumors (2). In this review, we discuss the current state of immunotherapeutic drug development in hematologic malignancies (HM) focused on targeting of immune checkpoints and the tumor microenvironment (TME), potential mechanisms of resistance to checkpoint blockade, and possible strategies for expanding the number of patients with HM who benefit from immune checkpoint directed therapies.

Biology of the immune checkpoints: focus on PD-1 and CTLA-4

Humans have evolved to maintain immune homeostasis through the use of multiple overlapping mechanisms aimed at preventing autoimmunity. In the adaptive immune system this requires a balance between recognition of non-self-antigen epitopes by naive T cell clones and the avoidance of recognition of self, a process that begins through positive and negative selection of developing T-cells in the thymus. Naïve T-cell activation initiates in the lymphatic system and hinges on T-cell receptor (TCR) recognition of antigen in the context of major histocompatibility molecules (MHC) and effective co-stimulation of CD28 by CD80/86 on antigen presenting cells (APCs). This in turn

results in CTLA-4 upregulation on the T cell, and through competitive binding to the co-stimulatory molecules CD80/CD86, negatively modulates activated T cells (3).

In the tissues, the interaction of the programmed cell death 1 receptor (PD-1, CD279) on activated T-cells with its ligands PD-L1 (B7-H1 or CD274) and PD-L2 (B7-DC or CD273) maintains immunologic tolerance through the suppression of auto-reactive T-cells. The clinical activity observed with PD-1 pathway blockade highlights its importance in tumor immune evasion and has led to clinical development of numerous antibodies that block the PD-1/PD-L1 pathway. APCs and tumor cells expressing PD-L1 can engage PD-1 on T cells resulting in T cell dysfunction and protection of PD-L1-expressing cells from T-cell mediated lysis (4,5) and in HMs tumor cell expression of PD ligands may be an inherent feature of disease biology (6). Although, identification of tumor types with PD-L1 expression in the TME identifies subsets of patients who benefit from checkpoint blockade, PD-1 ligand expression does not guarantee a response nor does its absence exclude the possibility of response to checkpoint blockade (7).

Clinical trials of immune checkpoint blockade in HM

CTLA-4 blockade

Ipilimumab and tremelimumab are two anti-CTLA-4 humanized IgG blocking antibodies currently in various stages of clinical development in solid tumor and HM (8,9). Ipilimumab led to clinical responses in metastatic melanoma leading to its FDA approval (10) and showed proof of concept for immune checkpoint blockade as a relevant strategy for drug development in oncology, which has subsequently been explored in solid tumors and multiple HM.

PD-1 blockade

PD-1 pathway blockade with nivolumab (11-15), pembrolizumab (16,17), atezolizumab (18), and durvalumab (MEDI4736) (19,20) has demonstrated activity in multiple solid tumor malignancies. Nivolumab and pembrolizumab are the two anti-PD1 agents in the most advanced stages of clinical development in HM. There are multiple additional agents designed to block PD-1 or PD-L1, which are in various earlier phases of clinical development.

PD-1 blockade in classical Hodgkin lymphoma (cHL)

TME in HL is composed of a dense-but-ineffective inflammatory infiltrate that is recruited to the tumor site by small numbers of Hodgkin Reed-Sternberg (HRS) cells (21). Near-universal genetic changes in chromosome locus 9p24.1 with corresponding PD-1 ligand upregulation through JAK-STAT signaling not only suggested a rationale for testing anti-PD-1 therapy, but appear to be a biologic determinant of presentation and survival in cHL (6). In a series of 108 biopsy specimens from patients with newly diagnosed cHL, 105 (97%) had increased expression of PD-1 ligands detected using immunohistochemistry (IHC) (6). In another 246 patient series with HL, PD-L1 expression by IHC was noted on ≥5% of tumor cells in 71% of cHL (166/233) and in 54% (7/13) of NLPHL (22). In patients with cHL and normal 9p24.1 copy number, PD-L1 could still be overexpressed due to Epstein-Barr virus (EBV) infection (23). These data strongly suggest a potential genetic dependence upon PD-1 signaling in cHL.

PD-1 antibody monotherapy in HL has demonstrated high and durable response rates in early clinical studies (*Table 1*). The phase I study of nivolumab in HL (NCT01592370) showed an 87% objective response rate, with 17% reaching CR and 70% achieving PR (28). The phase II CheckMate 205 study (NCT02181738) of nivolumab in patients with relapsed/refractory (R/R) cHL after failed autologous stem cell transplant (ASCT) and brentuximab vedotin demonstrated an objective response rate of 66%% (53/80 patients, 95% CI: 54.8–76.4%), with 7 patients achieving a complete remission (9%) and 46 patients reaching a partial remission (58%) (30). The median duration of response was 8.7 months, with a median time to response of 2.1 months (range: 0.7–5.7 months) (28,30). High-level alterations of 9p24.1 and increased PD-L1 expression, although previously shown to be linked with chemoresistance and inferior outcomes in cHL, appear to be associated with more favorable responses to treatment with nivolumab (6,30).

Pembrolizumab has also shown significant efficacy in R/R cHL patients as well. Updated results from KEYNOTE-013 (n=31) with a median follow-up of 24.9 months showed ORR 58% (18/31), CR 19% (6/31), and 12% achieving PR (12/31), with median duration of response not yet reached (25). In the phase II KEYNOTE-087 study (n=205), pembrolizumab was evaluated in 3 cohorts of cHL patients defined by history of exposure to brentuximab vedotin and ASCT. Pooled preliminary data from the three groups showed an ORR of 65.4–68.3%, CRR of 21.7–29%, and 93.7% had reduced

Table 1 Results of checkpoint blockade in classical Hodgkin lymphoma (cHL)

Disease	Drug	Target	Phase	Patients	ORR (%)	PD	SD	PR	CR	PFS	OS	DOR	References
cHL (R/R), (post-Bv)	Pembrolizumab (KEYNOTE-013, NCT01953692)	Anti-PD-1	Ib	31	65	13%	7 (23%)	12 (39%)	6 (19%)	24 weeks: 69%	NR	71% ≥24 weeks	(24,25)
cHL (R/R) post-ASCT, 3 cohorts: (I) Bv exposed; (II) Bv failure; (III) no Bv exposure	Pembrolizumab (KEYNOTE-087, NCT02458594)	Anti-PD-1	II	Cohort 1: 30; Cohort 2: 30; Cohort 3: accrual ongoing	Cohort 1: 66.7; Cohort 2: 65.4; Cohort 3: 68.8	NR	NR	Cohort 1: n=15 (50%); Cohort 2: n=16 (53%); Cohort 3: not reported	Cohort 1: 29%; Cohort 2: 24.7%; Cohort 3: 21.7%	NR	NR	NR	(26,27)
cHL (R/R)	Nivolumab (CheckMate 039, NCT01592370)	Anti-PD-1	I	23	87	0	3 (13%)	14 (70%)	6 (26%)†	Median not reached	91% at 1 year, 83% at 18 months	NR	(28,29)
cHL	Nivolumab (CheckMate 205)	Anti-PD-1	II	80	66	NR	NR	57.5%	8.8%	6-month PFS 77%	6mo OS 99%	NR	(30)
cHL (R/R) after allo-HSCT	Ipilimumab	Anti-CTLA-4	I	14	14	NR	NR	NR	2 (14%)	NR	NR	NR	(31)
cHL (R/R) after allo-HSCT	Ipilimumab	Anti-CTLA-4	I/Ib	7	14	NR	3 (43%)	1 (14%)	NR	NR	NR	NR	(32)

ORR, overall response rate; PR, partial response; CR, complete response; DOR, duration of response; PFS, progression free survival; OS, overall survival; NR, not reached; cHL, classical Hodgkin lymphoma; Bv, brentuximab vedotin; PD-1, programmed death-1; R/R, relapsed/refractory; IRRC, independent radiologic review committee. †, one patient achieved CR again after retreatment with nivolumab when relapse occurred within 1 year of discontinuing treatment following an initial CR.

tumor burden. The most common treatment related AEs were pyrexia (11%), hypothyroidism (10.5%), diarrhea (6.7%), fatigue (6.7%), headache (6.2%) rash (6.2%) and nausea (5.7%). This preliminary study shows significant clinical activity of pembrolizumab in all three cohorts, including chemo-refractory patients with cHL.

Long term follow-up safety data showing acute GVHD in 82% (14/17) of cHL patients treated with nivolumab who went on to allogeneic hematopoietic stem cell transplant (allo-HSCT) after participation in CheckMate 039 (n=5) and CheckMate 205 (n=12) suggest anti-PD-1 exposure prior to allo-HSCT may amplify risk of immune related complications after allogeneic transplantation. Grade 2–4 GVHD was seen in 10/17 (59%) and grade 3–4 in 5/17 (29%), with median time to onset of GVHD of 22 days. Two patients had hyperacute GVHD ≤14 days after transplant, and one patient with hepatic veno-occlusive disease died from multi-organ GVHD. Although numbers are small, these findings warrant studies of larger cohorts of patients with longer follow-up periods to understand risk and etiology of GVHD in patients who go on to allo-HSCT after PD-1 blockade (33).

In sum, these results led to accelerated FDA approval for nivolumab in cHL refractory to ASCT and brentuximab in May 2016 contingent upon a confirmatory phase III study. Results from a regulatory agency review of pembrolizumab data in cHL are expected soon. Practitioners are cautioned about allogeneic transplant following PD-1 pathway blockade due possible signal of increased risk of GVHD in this setting.

Other phase I and II clinical trials are currently underway in cHL comparing regimens with combinations of nivolumab with brentuximab (NCT02572167), nivolumab, ipilimumab, and brentuximab (NCT01896999) and nivolumab with ibrutinib (NCT02940301). Preliminary results from the CheckMate039 study of nivolumab plus ipilimumab were presented at ASH 2016, with an ORR in HL of 74% (n=23/31), with 6/31 reaching CR (19%), and 17 achieving PR (55%) (34). Preliminary response data from the ECOG-ACRIN E4412 study of combination therapy with brentuximab, ipilimumab, and nivolumab was also presented at ASH 2016, with an observed ORR of 100% in evaluable patients receiving brentuximab plus nivolumab, with CR rate of 62.5% (5/8), with 2 patients with prior brentuximab exposure achieving CR (35). There are also data exploring novel combinations of PD-1 agents with epigenetic modifiers in patients with refractory cHL (36). Clinical development of anti-PD-1 therapy in cHL continues, with a planned phase III of nivolumab monotherapy for cHL, and a phase III trial comparing pembrolizumab head-to-head with brentuximab (KEYNOTE-204, NCT02684292) as well as studies evaluating treatment with PD-1 blockade earlier in the natural history of cHL.

PD-1 blockade in non-Hodgkin lymphoma (NHL)

PD-L1 expression was found to be abundant in aggressive B-cell lymphoma, viral-associated lymphomas, and immunodeficiency-related lymphomas (37). Similar to cHL, primary mediastinal B cell lymphoma (PMBL), T-cell/histiocyte rich large B cell lymphoma, EBV+ DLBCLs such as DLBCL of the elderly and EBV+ immunodeficiency-associated lymphomas had 90–100% PD-L1/L2 expression driven by 9p24.1 gene amplification (38,39). Other subtypes of lymphoma noted to have PD-L1 expression include extranodal NK/T-cell lymphoma (83%), primary effusion lymphoma (75%), EBV(+) post-transplant lymphoproliferative disorder (PTLD, 70%), EBV(–) PTLD (57%), plasmablastic lymphoma (44%), and DLBCL-NOS (14%) (38). Primary testicular lymphoma, primary CNS lymphoma, mediastinal gray zone lymphoma and some T-cell lymphomas also have been reported to have 9p24.1 gene amplification and related PD-L1/PD-L2 overexpression (38). In addition to 9p24.1 amplification, there have also been translocations identified involving PD-L1 and PD-L2 in primary testicular lymphoma and primary CNS lymphoma (40).

In follicular lymphoma (FL), PD-1 expression in $CD4^+$ tumor infiltrating lymphocytes (TILs) is associated with unresponsiveness to cytokines, a state consistent with T cell exhaustion (41). However, peripheral T cells and $PD1^-$ T cells exhibited normal activation upon exposure to cytokines (41). Although FL cells do not express PD1 ligands, histiocytes in the TME in FL do express PDL1, and suggest a potential rationale for use of anti-PD1 antibody in FL (41). Although PD1 is typically used to define exhausted T cells, it is highly expressed in T follicular helper cells, and has differential expression among exhausted T cells (42). Additional markers of T-cell exhaustion such as TIM-3 and LAG-3 are co-expressed with PD-1 in exhausted T cells, and represent potential targets for combination immunotherapy that can reverse T cell exhaustion, and as proof of concept that may be explored in future clinical trials, reversal of T cell exhaustion signaling has been demonstrated *in vitro* with anti-PD-1 and anti-LAG-3 (42,43).

Clinical evaluation of PD-1/PD-L1 blockade in NHL has been limited to phase I studies inclusive of multiple

types of HM and some phase II studies demonstrating activity in DLBCL and FL (*Table 2*).

Pidilizumab, a humanized IgG1 monoclonal antibody intended to block PD-1, was evaluated in a phase II study of 66 patients with DLBCL after ASCT. This study had an ORR of 51%, with 70% of patients without PD at 16 months (46). A study of pidilizumab plus rituximab in 32 patients with relapsed FL demonstrated an ORR of 66% (19/29 evaluable patients) and 15 CRs were noted (52%) (47). Pidilizumab's clinical development has been delayed by doubts about its target, as it does not bind PD-1 (49). Nivolumab monotherapy in FL showed a 40% ORR (4/10), with 1 CR (n=1, 10%), 3 PR (n=3, 30%), and 6 with stable disease (n=6, 60%), with median PFS not reached (NCT01592370) (44). The KEYNOTE-013 study included 19 patients with PMBL where pembrolizumab showed a response rate of 41%, with 2 patients achieving CR and 5 achieving PR (50). A phase II study (KEYNOTE-170) is planned based on these results.

In T cell NHL (T-NHL), pembrolizumab has shown clinical activity in advanced stage R/R mycosis fungoides (MF) and Sézary syndrome (SS), with ORR of 38% with 1 CR and 8 PRs (48). The CheckMate 039 study included 23 patients with T-NHL treated with nivolumab monotherapy in which there were 4 PRs, 2/13 in MF and 2/5 in peripheral T cell lymphoma (PTCL) (44). A recent series demonstrated a high rate of response to pembrolizumab in NK/T cell lymphoma (51). Multiple studies of immune checkpoint blockade are ongoing in several subtypes of NHL (*Table 3*).

Varying levels of PD-1/PD-L1 expression in the TME are noted in NHL (37). Evaluation of PD-L1 expression in a small series of patients with aggressive B-cell NHL found that 3/7 responders (2 CRs, 1 PR) had high PD-L1 expression (30–100%) (52). Thus, in these preliminary analyses, PD-L1 IHC does not appear to consistently predict for responses.

Blockade of immune checkpoints in plasma cell myeloma

The myeloma TME

Multiple myeloma (MM) is a complex malignancy arising from plasma cells located within the bone marrow with known humoral and cellular immunodeficiency. MM is characterized by clonally heterogeneous malignant plasma cell populations that proliferate and persist in the bone marrow TME. The MM TME is comprised of osteoblasts, osteoclasts, bone marrow stromal cells (53), an immunosuppressive milieu of cytokines (54-58), myeloid-derived suppressor cells (MDSC) (59,60), regulatory T cells (61-63), and active PD-1/PD-L1 signaling, all of which contribute to local immune dysfunction and dysregulation.

In addition to the role played by other immune cells, MM cells directly contribute to cellular immune dysfunction. MM cells express HLA class II and may participate in cross-presentation of antigens and induction of immune tolerance to tumor antigens (64). MM cells can also express PD-L1, whereas normal plasma cells do not (65). PD-L1 expression on MM cells is associated with reduced susceptibility to cytotoxic effector T cell killing (65). PD-L1/PD-L2 expression in MM cells is driven by IFN-γ, toll-like receptor (TLR), Akt, and Ras signaling (65,66). Global defects in innate and adaptive immunity in myeloma include B cell dysfunction (hypogammaglobulinemia), abnormal dendritic cell (DC) number and function (67), natural killer (NK) (68-70), natural killer T-cell (NKT) (71), and T cell dysfunction (71,72). T cells in MM patients have been shown to have reduced cytotoxicity (73) and responsiveness to interleukin 2 (IL-2) (74), with alteration of the quantity and distribution of T cell subsets (63,75,76). APC in MM are also abnormal; DC isolated from myeloma patients have been shown to be functionally impaired (67). Plasmacytoid dendritic cells (pDC) are increased in the MM BM TME compared with healthy controls, and these cells are less able to trigger T cell proliferation (77). Despite multifactorial local immunosuppression in the MM TME, marrow-infiltrating T cells isolated from the MM TME retain the capacity to develop specific anti-MM immunity, demonstrated through *ex vivo* priming of T cells by DC that have processed tumor cell antigen outside the confines of the local MM TME (78).

In preclinical studies, syngeneic mice lacking PD-1 completely suppress growth of a MM tumor cell line (J558L), whereas mice expressing PD-1 rapidly develop tumor (79), suggesting a potential role for PD-1 blockade in treatment of myeloma. In the 5T33 model of myeloma, use of an anti-PD-L1 antibody in combination with lymphodepletion with radiation and a vaccine led to anti-myeloma activity (80). This effect was abrogated by depletion of CD4 or CD8 T cells, indicating that presence and function of both T cell subsets are necessary for this effect (80,81).

Although preclinical data supports a rationale for PD-1 blockade, nivolumab monotherapy did not show clinical efficacy (44) (*Table 4*). However, given that T cells are indeed capable of recognizing and killing MM cells, exploration of potential combinations with drug partners

Table 2 Clinical trials of checkpoint blockade in non-Hodgkin lymphoma (NHL)

Disease	Drug	Target	Phase	Patients	ORR	PR	CR	PFS	OS	DOR	References
Diffuse large B cell lymphoma (DLBCL)											
DLBCL	Nivolumab	Anti-PD-1	I	11	4 (36%)	3 (27%)	1/11 (9%)	NR	NR	22 weeks	(44)
DLBCL	Pidilizumab 0.2-6.0 mg/kg	Unknown	I	2	0%	0	0	NR	NR	NR	(45)
DLBCL, PMBL, transformed indolent lymphoma, after auto-HSCT	Pidilizumab 1.5 mg/kg every 42 days, 30-90 days after auto-HSCT	Unknown	II	66	51%	6 (17%)	12 (34%)	72% at 16 months	NR	NR	(46)
Follicular lymphoma (FL)											
FL (treatment-naïve)	Pidilizumab 3 mg/kg	Unknown	I	1	100%	0	1 (100%)	NR	NR		(45)
FL	Nivolumab	Anti-PD-1	I	10	40%	3 (30%)	1 (10%)	NR	68% at 24 weeks	MNR	(44)
FL (R/R)	Pidilizumab + rituximab	Unknown, anti-CD20	II	32 (29 evaluable)	19 (66%)	4 (14%)	15 (52%)	NR	NR	Median 20.2 months	(47)
Other B-NHL											
PMBL	Nivolumab	Anti-PD-1	Ib	2	100% (SD)	NR	NR	24 weeks: 100%	NR		(44)
T-NHL											
CTCL	Nivolumab	Anti-PD-1	I	13	15%	15%	0%	NR	NR	MNR	(29)
PTCL	Nivolumab	Anti-PD-1	I	5	40%	0%	0%	NR	NR	MNR	(29)
Sézary Syndrome (SS); Mycosis Fungoides (MF)	Pembrolizumab	Anti-PD-1	II	24 total (SS =18; MF n=6)	SS: 33%; MF: 50%	SS: 33%; MF: 33%	SS: 0; MF 17%	12-month PFS: 69%	MNR	MNR	(48)

PMBL, primary mediastinal B cell lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; CTCL, cutaneous T cell lymphoma; PTCL, peripheral T cell lymphoma; SS, Sézary syndrome; MF, mycosis fungoides; SD, stable disease; RR, response rate; PR, partial response; CR, complete response; PFS, progression free survival; OS, overall survival; MNR, medial not reached; NR, not reported; ASCT, autologous stem cell transplant.

Table 3 Select ongoing and upcoming immune checkpoint studies in lymphoma

NCT (name)	Diseases	Checkpoint inhibitor(s)	Phase	Combination therapy	Status	Est. primary completion date	Est. study completion date
CTLA-4							
NCT01896999	R/R cHL	CTLA-4, PD-1	I	Ipilimumab plus nivolumab plus brentuximab vedotin	Open, recruiting	06/2018	NR
NCT01822509	Relapsed heme malignancies after allo HSCT	CTLA-4, PD-1	I/Ib	Single agent nivolumab or ipilimumab	Open, recruiting	12/2016	NR
NCT02549651	DLBCL	CTLA-4, PD-1	I	Durvalumab + Tremelimumab or AZD9150	Open, recruiting	07/2021	07/2021
NCT02643303	CTCL	CTLA-4, PD-1, TLR3 agonist	I/II	Intratumoral tremelimumab, + IV durvalumab + IT/IV polyICLC (TLR3 agonist)	Open, recruiting	08/2022	08/2022
NCT02681302	Lymphoma	Ipilimumab, nivolumab	I/II	Ipi, Nivo, alone or in combination after auto-HSCT	Not yet open	08/2017	08/2018
PD-1							
NCT02327078	DLBCL, HL	Nivolumab, Epacadostat	I/II	Epacadostat with nivolumab	Open, recruiting	04/2019	10/2019
NCT02332980	Low grade B-NHL	Pembrolizumab	II	Pembrolizumab ± idelalisib or ibrutinib	Open, recruiting	01/2020	NR
NCT02362997	HL, DLBCL	Pembrolizumab	II	Pembrolizumab post auto-HSCT	Open, recruiting	07/2018	12/2018
NCT02684292 (KEYNOTE-204)	R/R cHL	Pembrolizumab	III	Pembrolizumab *vs*. Brentuximab vedotin	Open, recruiting	02/2018	08/2019
NCT02950220	R/R NHL	Pembrolizumab	I	Pembrolizumab + ibrutinib	Not yet open	12/2019	NR
NCT02973113 (PREVALE)	R/R EBV+ Lymphomas	Nivolumab	I	Nivolumab + EBV-specific T cells (EB-VSTS)	Not yet open	02/2019	02/2020
NCT02253992	B-NHL	Nivolumab, Urelumab	I/II	Urelumab (CD-137 mAb) + nivolumab	Open, recruiting	122018	09/2019
NCT02740270	Lymphoma	PDR001, GWN323	I	GWN323 (anti-GITR) ± PDR001	Open, recruiting	05/2019	05/2019
PD-L1							
NCT02220842	R/R FL or DLBCL	Atezolizumab	I	Atezolizumab + obinutuzumab	Open, recruiting	05/2019	05/2019
NCT02729896	R/R FL or DLBCL	Atezolizumab	I	Obinutuzumab, polatuzumab vedotin, atezolizumab	Open, recruiting	07/2020	07/2020
NCT02596971	FL or DLBCL	Atezolizumab	I	Atezolizumab + obinutuzumab/ bendamustine or obinutuzumab-CHOP	Open, recruiting	01/2020	01/2020

Table 3 *(continued)*

Table 3 *(continued)*

NCT (name)	Diseases	Checkpoint inhibitor(s)	Phase	Combination therapy	Status	Est. primary completion date	Est. study completion date
NCT02631577	R/R FL	Atezolizumab	I	Atezolizumab with obinutuzumab + lenalidomide	Open, recruiting	01/2020	01/2020
NCT02603419	R/R cHL	Avelumab	Ib	N/A	Open, recruiting	09/2017	09/2017
NCT02951156	R/R DLBCL	Avelumab	Ib/III	3 cohorts: Avelumab PLUS: itolizumab/ rituximab, itolizumab/azacitidine, or rituximab-bendamustine, phase III with winner	Open, recruiting	02/2021	02/2021
NCT02733042 (FUSION NHL 001)	NHL, CLL	Durvalumab	I/II	4 arms: durvalumab ± rituximab-lenalidomide, ibrutinib, rituximab-bendamustine	Open, recruiting	12/9/2016	12/9/2016

R/R, relapsed/refractory; DLBCL, diffuse large B cell lymphoma; CTCL, cutaneous T cell lymphoma; IV, intravenous; HSCT, hematopoietic stem cell transplant; EBV, Epstein Barr virus; B-NHL, B cell non-Hodgkin lymphoma; FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; NR, not reported; N/A, not applicable.

Table 4 Results of checkpoint blockade in multiple myeloma

Disease setting	Drug	Target/Mechanism of action	Phase	Patients	ORR	PR	≥ VGPR	PFS	OS	References
MM (R/R)	Nivolumab	Anti-PD-1	Ib	27	0 (0%)*	0	0	NR	NR	(44)
MM, no prior treatment	Pidilizumab	Anti-PD-1	Ib	1	0, SD for >13 months	0	0	NR	NR	(45)
MM (R/R)	Pembrolizumab, lenalidomide, dexamethasone; KEYNOTE-023 (NCT02036502)	Anti-PD-1	I	50 (17 evaluable)	17 (76%)	5 (56%)	NR	NR	NR	(82)
MM (R/R)	Pembrolizumab, pomalidomide, dexamethasone (NCT02289222)	Anti-PD-1	II	48	27/48 (56%)	14 (29%)	13(27%)	NR	NR	(83)
MM (R/R) with prior pomalidomide exposure (retrospective study)	Pembrolizumab, pomalidomide, dexamethasone	Anti-PD-1	II	9	33%	3	0	Median 57 days	56% at 6 months	(84)

*One patient achieved CR following radiation therapy to a focal bony lesion that developed while on nivolumab. MM, multiple myeloma; R/R, relapsed/refractory; SD, stable disease; ORR, overall response rate; PR, partial response; VGPR, very good partial response; PFS, progression free survival; OS, overall survival; NR, not reported.

that might synergize with immune checkpoint blockade through modulation of the TME is an area of active drug development in MM. Several classes of anti-myeloma drugs exert immunomodulatory effects upon the TME and may synergize with immune checkpoint blockade and represent rational partners for immunotherapy drug development in MM. Immunomodulatory drugs (IMiDs) such as lenalidomide, pomalidomide, and thalidomide enhance anti-myeloma cellular immunity by augmenting T cell responsiveness to APCs, polarizing T cells towards a Th1 phenotype (85), inhibiting proliferation and function of Tregs (86), down-regulating PD-L1, and augmenting NK cell function. Lenalidomide has been shown to synergize with PD-1/PD-L1 blockade to inhibit immune suppression mediated by MDSC and enhance NK cell cytotoxicity in MM (60,87), and these agents through their action on the immune system are rational partners for use with immune checkpoint inhibition in MM.

Monoclonal antibodies against CD38 have entered clinical use for myeloma with the FDA approval of daratumumab for relapsed MM and its role in the TME may provide rationale for use of anti-CD38 antibodies in combination with immune checkpoint blockade. CD38 has pleiotropic expression and effects, mediating T cell anergy and exhaustion, and drives immunosuppressive activity of MDSC and Tregs (88-90). Use of daratumumab depletes CD38+ MDSC and Tregs in the TME and leads to expansion and skewing of T cell repertoire in patients with MM (91), suggesting that daratumumab partnered with immune checkpoint blockade might further activate T cells and drive anti-myeloma immune responses.

NK cells play an important role in the immune defense against myeloma (92), and blockade of inhibitory KIR receptors on NK cells is under evaluation as a therapeutic strategy in myeloma. KIRs are cell surface receptors present on both NK cells and some T cell subsets that recognize MHC class I molecules and modulate cell-mediated cytotoxicity (93). MM cells express surface ligands that bind to inhibitory KIRs and drive NK cell dysfunction (94), and there are studies underway to evaluate the potential to block inhibitory KIR signaling and restore MM-directed NK cell cytotoxicity. IPH2101, a human IgG4 against KIR2D inhibitory receptor, showed no objective responses and stable disease in 34% of RRMM patients, with no significant toxicity (95), and showed no single-agent activity in a phase II study of patients with smoldering MM (96). IPH2101 was also evaluated in combination with lenalidomide in 15 patients with R/R MM, and led to 5 objective responses (≥ MR): 2 VGPRs, 3 PRs, 1 MR, and 6 patients had SD (NCT01217203) (97). Lirilumab is a second-generation anti-KIR monoclonal antibody now in development in combination with elotuzumab (NCT02252263) and in combination with nivolumab (NCT01592370) in patients with R/R MM and lymphomas.

Ongoing and future drug combinations in MM

Ongoing clinical trials of IMiDs combined with PD-1 pathway blockade have shown promising preliminary results. The phase I KEYNOTE-023 (NCT02036502) study of pembrolizumab plus lenalidomide and dexamethasone in relapsed MM showed an overall response rate of 76% in 17 evaluable patients, with 5 patients achieving a PR or better (56%) (82). A phase II study (NCT02289222) combining pembrolizumab, pomalidomide, and dexamethasone had an ORR of 56% (27/48), ORR 55% among patients double-refractory to both proteasome inhibitors and IMiDs, and ORR 33% among patients with high-risk cytogenetics (98). Pembrolizumab, pomalidomide, and dexamethasone evaluated in a phase II study enrolling 48 patients with R/R MM, among which the overall response rate was ≥PR in 27 of 48 patients (55%), including sCR (n=4, 8%), nCR (n=3, 6%), VGPR (n=6, 13%), PR (n=14, 29%), and 7 minimal responses (15%), stable disease (n=9, 19%), 2 with progressive disease and 3 patients were not evaluable for response (83). Interestingly, responses correlated with presence of bone marrow infiltrating $CD8^+$ effector T cells [ASH 2016 oral presentation (83)]. A retrospective series also supports the activity of this combination in a heavily pretreated and pomalidomide-exposed population, with an ORR of 33%, with 89% of patients achieving clinical benefit (3 PR, 2 MR, 3 SD) (84).

Building on the preliminary results of studies showing efficacy of approaches combining anti-myeloma drugs with immune checkpoint inhibitors discussed above (*Table 4*), several phase II and III clinical trials are planned and ongoing (*Table 5*). The phase III KEYNOTE-185 study of lenalidomide plus dexamethasone with or without pembrolizumab is planned (NCT02579863), and the phase III KEYNOTE-183 study (NCT02576977) is accruing R/R MM patients to evaluate pembrolizumab with or without pomalidomide and dexamethasone. A cohort in the CheckMate 039 study (NCT01592370) is currently enrolling patients to evaluate nivolumab plus daratumumab *vs.* nivolumab plus daratumumab, pomalidomide, and dexamethasone in R/R MM. Nivolumab, elotuzumab, pomalidomide, and dexamethasone will be evaluated

Table 5 Select open and upcoming immune checkpoint trials in MM and plasma cell disorders

NCT (name)	Disease/population	Checkpoint inhibitor(s)	Phase	Combination therapy	Status	Est. primary completion	Est. study completion
CTLA-4							
NCT01822509	Relapsed heme malignancies after allo-HSCT	CTLA-4, PD-1	I/Ib	N/A	Open, recruiting	12/2016	NR
NCT02716805	MM at high risk for relapse	CTLA-4, PD-1	I	Durvalumab, tremelimumab with auto-HSCT	Open, recruiting	06/2019	06/2021
PD-1							
NCT01592370	MM	Nivolumab or ipilimumab combinations	I	Nivolumab, ipilimumab, lirilumab, daratumumab, pomalidomide, dexamethasone	Open, recruiting	10/2018	03/2020
NCT02331386	MM (high risk)	Pembrolizumab	II	Pembrolizumab + lenalidomide post auto-HSCT	Not yet recruiting	07/2018	07/2019
NCT02603887	Smoldering multiple myeloma	Pembrolizumab	Pilot	Pembrolizumab monotherapy	Open, recruiting	07/2019	NR
NCT02576977 (KEYNOTE-183)	R/R MM	Pembrolizumab	III	Pomalidomide + low dose dexamethasone ± pembrolizumab	Open, recruiting	07/2018	07/2018
NCT02880228	Newly diagnosed MM (transplant-eligible)	Pembrolizumab	II	Pembrolizumab/lenalidomide/dexamethasone	Open, recruiting	12/2021	NR
NCT02579863 (KEYNOTE-185)	Newly diagnosed MM	Pembrolizumab	III	Lenalidomide/dexamethasone ± pembrolizumab	Open, recruiting	10/2018	03/2019
NCT02036502 (KEYNOTE-023)	MM	Pembrolizumab	I	Pembrolizumab in combination with standard of care treatments	Open, recruiting	10/2019	10/2019
NCT02636010	MM with residual disease	Pembrolizumab	II	Pembrolizumab monotherapy	Open, recruiting	07/2019	01/2020
NCT02077959	R/R MM	Pidilizumab	I/II	Lenalidomide + pidilizumab	Open, recruiting	06/2017	NR
PD-L1							
NCT03000452	R/R MM	Durvalumab	II	Daratumumab + durvalumab	Not yet open	07/2020	07/2020
NCT02685826	Newly diagnosed MM	Durvalumab	I	Durvalumab/lenalidomide with or without dexamethasone	Open, recruiting	04/2022	08/2024
NCT02616640	R/R MM	Durvalumab	I	Durvalumab monotherapy or in combination with pomalidomide ± dexamethasone	Open, recruiting	12/2016	11/2017
NCT02886065	Smoldering multiple myeloma	Durvalumab	I	Durvalumab and PVX-410 (multi-peptide cancer vaccine) ± lenalidomide	Not yet open	09/2019	09/2021
NCT02784483	Asymptomatic MM/smoldering multiple myeloma	Atezolizumab	I	N/A	Open, recruiting	12/2018	06/2019
NCT02431208	MM	Atezolizumab	I	Atezolizumab ± IMiD/daratumumab or daratumumab	Open, recruiting	08/2019	08/2018
Pending	Solitary bone plasmacytoma	Durvalumab	Pilot	Concurrent durvalumab + definitive radiation therapy to plasmacytoma	Not yet open	NR	NR

MM, multiple myeloma; allo-HSCT, allogeneic hematopoietic stem cell transplant; R/R, relapsed/refractory; auto-HSCT, autologous hematopoietic stem cell transplant; SD, stable disease; ORR, overall response rate; PR, partial response; VGPR, very good partial response; PFS, progression free survival; OS, overall survival; NR, not reported; N/A, not applicable.

in CheckMate 602 (NCT02726581). There are also trials underway in smoldering MM (pembrolizumab, NCT02603887; nivolumab plus lenalidomide and dexamethasone, NCT02903381). Studies are enrolling patients for treatment with ipilimumab plus nivolumab after ASCT (NCT02681302) and after allo-HSCT (NCT 01822509). A study evaluating durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4) after ASCT is also underway (NCT02716805).

In summary, combination approaches using immune checkpoint inhibitors and anti-myeloma drugs has shown activity in preliminary results from several clinical trials, and studies of multiple combinations of anti-myeloma agents and immune active compounds are planned or underway.

Checkpoint blockade in chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and myelodysplasia

Although the vast majority of clinical data using checkpoint blockade in HM thus far has been in lymphoid cancers, a significant body of preclinical work supports exploration of the value of immune checkpoint inhibition in myeloid disorders. CTLA-4 is expressed on the malignant cell surface and in the cytoplasm in most patients with AML (99), chronic myeloid leukemia (CML), and CLL (100). Patients with AML with the CTLA-4 CT60 AA genotype have worse outcomes and higher rates of relapse after induction therapy in the first complete remission, suggesting potential impaired immune control of minimal residual disease after induction therapy (99). The PD-1 pathway plays a role in immune escape in CML (101). PD-1 is expressed on CLL cells in higher levels than in healthy controls, but PD-1 expression levels did not carry prognostic value in CLL (102). PD-L1 expression on CLL cells has been associated with impaired function of the immune synapse with T cells (103).

In the myelodysplastic syndrome (MDS), there is evidence that PD-1 pathway blockade may be a promising avenue for treatment. PD-L1 is expressed at higher levels on blasts in patients with high risk MDS and more refractory disease. Additionally, there are data that azacitidine upregulates PD-1 and PD-L1 in MDS and that this is associated with emergence of resistance to azacitidine (104).

Thus far, clinical experience using immune checkpoint blockade in patients with leukemia is limited to early phase clinical trials (*Table 6*). In a phase I study of pidilizumab, 8 patients with AML were included, of which 7 of 8 had no change in average percentage of blasts in peripheral blood at 21 days, and one of 8 patients had a response, with peripheral blasts percentage dropping to 5% from 50%, and who ultimately had disease progression 61 weeks after receiving pidilizumab (45). In patients with previously treated or untreated MDS, a phase II study is ongoing evaluating the combination of nivolumab or ipilimumab with 5-azacitidine study (105). Preliminary results showed that single agent ipilimumab is capable of inducing responses in previously treated MDS patients (ORR 22%), however, single agent nivolumab showed no clinical activity (105). Azacitidine plus nivolumab had an ORR of 69% (9/13) in those patients who previously failed azacitidine treatment (105). Early phase studies evaluating ipilimumab in pan-HM with relapse after allo-HSCT have shown a low rate of response in lymphoma, with some responses seen in patients with myeloid disorders. Bashey *et al.* carried out a phase I study of ipilimumab in patients with recurrent or progressive HM after allogeneic stem cell transplant, enrolling 29 patients and evaluating for safety and efficacy as the primary outcome (31). Patients were treated with ipilimumab 10 mg/kg every 3 weeks, and notably 4 of 5 patients with extramedullary AML involving the skin (leukemia cutis) achieved a durable CR lasting more than 1 year (31). In the post-allo-HSCT setting, there has not been significant evidence of induction or worsening of graft versus host disease (GVHD) (31,32). Six patients in this study patients (21%) had immune-related adverse events (irAE), 4 patients (14%) had GVHD precluding further use of ipilimumab, and there was one death attributable to therapy (32). Based on these early results, CTLA-4 blockade after allogeneic stem cell transplant is undergoing additional study. Secondary endpoint data analysis showed CTLA-4 blockade by a single infusion of ipilimumab increased $CD4^+$ and $CD4^+$/HLA-DR^+ T lymphocyte counts and augmented intracellular CTLA-4 expression at the highest dose level. There was no significant change in Treg cell numbers after ipilimumab infusion (106).

Current ongoing studies target relapsed leukemia patient population and evaluate safety and effect of single immune checkpoint inhibitor use (nivolumab and ipilimumab), single versus combined immune checkpoint inhibitor use, novel combinations using checkpoint antibodies with other immunotherapeutic approaches such as the engineered bi-specific antibody (BiTE) against CD3 and CD19 (blinatumomab), and combined use of epigenetic

Table 6 Select open and upcoming immune checkpoint trials in leukemia and myeloid disorders

NCT (name)	Diseases	Checkpoint inhibitor(s)	Phase	Combination therapy	Status	Est. primary completion date	Est. study completion date
CTLA-4							
NCT02890329	R/R MDS or AML	Ipilimumab	I	Ipilimumab + decitabine	Not yet open	11/2019	NR
NCT01919619	Leukemia, Lymphoma	Ipilimumab	Pilot	Lenalidomide + ipilimumab post allo- or auto-HSCT	Not yet open	03/2019	NR
NCT01822509	Relapsed heme malignancies after allo-HSCT	CTLA-4, PD-1	I/Ib	N/A	Open, recruiting	12/2016	NR
NCT02846376 (CPIT-002)	AML, MDS	Ipilimumab, nivolumab	I	Ipilimumab, nivolumab, alone or in combination after allo-HSCT	Not yet open	08/2017	08/2018
NCT02530463	MDS	Ipilimumab, nivolumab	II	Ipilimumab and/or nivolumab, with or without azacitidine	Open, recruiting	09/2021	NR
PD-1							
NCT02879695	Poor Risk R/R CD19+ B-ALL	Nivolumab, Ipilimumab	I	Blinatumomab and nivolumab ± ipilimumab	Not yet recruiting	03/2019	NR
NCT02532231	AML	Nivolumab	II	Nivolumab	Open, recruiting	10/2018	NR
NCT02767934	B and T ALL	Pembrolizumab	II	N/A	Not yet open	01/2019	NR
NCT02771197	AML (non-transplant eligible)	Pembrolizumab	II	Fludarabine, melphalan, pembrolizumab	Open, recruiting	10/2018	10/2020
NCT02332980	R/R CLL	Pembrolizumab	II	Pembrolizumab ± idelalisib or ibrutinib	Open, recruiting	01/2020	NR
NCT02819804	R/R Ph+ ALL	Nivolumab	Ib	Nivolumab + dasatinib	Open, recruiting	07/2019	NR
NCT02767934	ALL	Pembrolizumab	II	N/A	Not yet open	01/2019	NR
NCT02845297	AML (R/R or newly diagnosed age ≥65 years old)	Pembrolizumab	II	Pembrolizumab + azacitidine	Open, recruiting	07/2020	07/2020
NCT02768792	AML, R/R	Pembrolizumab	II	High Dose Ara-C followed by pembrolizumab	Open, recruiting	06/2019	05/2021
NCT02708641	AML post-remission age ≥60 years old	Pembrolizumab	II	N/A	Not yet recruiting	06/2019	06/2021
NCT02535286	R/R CLL	Pembrolizumab	I/II	Ublituximab, TGR-1202	Open, recruiting	11/2017	12/2017
NCT02599649	MDS	Nivolumab	II	Lirilumab and Nivolumab with 5-Azacitidine	Open, recruiting	03/2025	NR
PD-L1							
NCT02892318	AML	Atezolizumab	I	Atezolizumab and guadecitabine	Open, recruiting	01/2019	01/2019
NCT02935361	R/R CMML, MDS, AML	Atezolizumab	I/II	Atezolizumab and guadecitabine	Not yet recruiting	11/2020	11/2021
NCT02846623	R/R or high risk untreated CLL	Atezolizumab	II	Atezolizumab with obinutuzumab and ibrutinib	Not yet recruiting	10/2020	NR

Table 6 *(continued)*

Table 6 *(continued)*

NCT (name)	Diseases	Checkpoint inhibitor(s)	Phase	Combination therapy	Status	Est. primary completion date	Est. study completion date
NCT02953561	R/R AML	Avelumab	I	Avelumab + azacitidine	Not yet recruiting	01/2017	01/2020
NCT02775903	Untreated high risk MDS or AML (elderly)	Durvalumab	II	Azacitidine (subcutaneous) + durvalumab	Open, recruiting	02/2018	04/2019
NCT02281084	MDS	Durvalumab	II	CC-486 (oral Azacitidine) + durvalumab	Open, recruiting	07/2018	01/2019
NCT02871323	Primary or secondary myelofibrosis	Durvalumab	I	N/A	Open, recruiting	11/2018	NR
Others							
NCT02835729	Newly diagnosed AML	Indoximod (IDO1)	I/II	Indoximod plus idarubicin and cytarabine	Open, recruiting	07/2018	NR
NCT02399917	R/R AML	Lirilumab	II	Lirilumab + 5-azacitidine	Open, recruiting	04/2020	NR
NCT02678338	R/R AML	Hu5F9-G4 (anti-CD47)	I	N/A	Open, recruiting	03/2017	01/2018
NCT02663518	R/R Heme malignancies	TTI-621 (anti-SIRPα)	I	N/A	Open, recruiting	06/2019	06/2019

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplant; B-ALL, B acute lymphoblastic leukemia; CLL, Chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; R/R, relapsed refractory; N/A, not applicable..

therapies with immune checkpoint inhibitors (decitabine and ipilimumab) (*Table 6*).

Immune-related adverse events and the checkpoint inhibitors

The phase I studies of nivolumab, pembrolizumab and pidilizumab demonstrate a favorable safety profile of these agents, with rates of drug related grade 3 adverse events ranging from 18–20% (28,44,45,107). IrAE were common and typically lower grade. There were 13/134 (9.7%) cases of pneumonitis, with three severe (grade 4) and one fatal case of pneumonitis observed (25,44-46,107). Although pulmonary toxicity is a known complication associated with treatment with PD-1 inhibitors (108), it is important to note in a patient population treated with agents with known potential for pulmonary toxicity such as radiation, carmustine, lenalidomide, pomalidomide, and bleomycin, there was not an excessive rate of pneumonitis noted in the phase I studies of PD-1 agents (109). Early data in melanoma suggests gut microbiota may play a role in development of colitis, however for the most part predictors of toxicity from immune checkpoint inhibitors are lacking (110).

Mechanisms of resistance to immune checkpoint blockade

Although a subset of patients with HM obtain benefit from treatment with immune checkpoints, mechanisms of resistance to these therapies remain poorly understood. Emerging data suggest alterations in MHC class I in the TME may limit tumors' responsiveness to immune-based approaches. Of note, a recent cohort study found that 75% (40/53) patients with DLBCL commonly fails to express HLA class I (111), and β2M mutations and deletions, and abnormalities in CD58 (a molecule involved in T cell and NK cell signaling), led to a lack of membrane HLA-I expression (111). Effector T-cells require intact MHC to bind the TCR in order to exert cellular cytotoxicity against tumor cells. It is logical to consider mutations causing reduced MHC expression on the tumor cell surface may affect response to immune checkpoint blockade. Beta-2 microglobulin (β2M) is a required component for assembly and surface expression of MHC class I, and a retrospective series evaluated β2M, MHC I, and MHC II expression, and found decreased or absent expression of β2M and MHC I in 80% and decreased or absent MHC class II in 70% of cHL patients. Reduced β2M and MHC

class I expression in cHL patients was associated with an inferior outcome independent of 9p24.1 status (112). The association of response to checkpoint blockade in patients with β2M, MHC class I, and MHC class II mutations have not yet been described in cHL. However, data from melanoma patients treated with PD-1 blockade demonstrating alterations in β2M and loss of MHC class I led to disease progression and resistance to PD-1 blockade immunotherapy (113), suggesting that efficacy of PD-1 blockade in cHL may be independent of antigen presentation by the malignant cell. Other mechanisms of resistance to immune checkpoint blockade, such as T cell exhaustion, inhibitory factors in the TME such as ADO and IDO, and novel mutations that mediate resistance remain active areas of investigation (114,115).

Novel immune checkpoints and combination therapies

Alternative immune cell co-receptors and targets in the immune microenvironment (beyond PD-1/PD-L1 and CTLA-4) represent potential opportunities for immunotherapy drug development and are in preclinical development or early phase clinical trials (*Table* 7) and are reviewed extensively elsewhere (2). In addition to blockade of immune checkpoints relevant to T-cell function, blockade of CD47, an innate immune checkpoint that inhibits phagocytosis by macrophages, has shown activity in multiple preclinical tumor models (116-122) as a potential drug target and several agents are in phase I clinical trials enrolling patients with HM (123,124). There is also intense interest in combinatorial approaches using cancer vaccines, chemotherapy, and radiation with immune checkpoint blockade to expand efficacy and response rates to checkpoint blockade, and novel clinical trials are underway to evaluate these approaches (125).

Conclusions

Development of immune checkpoint inhibitors is an important advance in the treatment of human cancers, and this approach has shown significant promise for treatment of a variety of HM. Novel drug combinations, identification of targets in the immune TME, and clinical trials of agents that modulate immune checkpoints beyond CTLA-4 and PD-1/PD-L1 are ongoing with the aim to expand the utility of immune-based approaches for treatment of all patients with lymphoid, plasma cell and

Table 7 The pipeline of immune checkpoint blockade and hematologic malignancies

Target	Symbol	Type of drug	Developer	Select Phase I Studies in HM
PD-1	Nivolumab (BMS-936558)	Fully human IgG4 mAb (whole antibody)	Bristol Myers Squibb	NCT01592370, NCT02985554, NCT01896999, NCT01822509
	Pembrolizumab (MK-3475)	Humanized IgG4 mAb (whole antibody)	Merck	NCT01953692, NCT02036502
	Pidilizumab*	Humanized (from mouse) IgG1 mAb	Medivation/CureTech	NCT02077959
	AMP-224	Recombinant B7DC-IgG1 Fc-Fusion protein	MedImmune/AstraZeneca	NCT01352884
	MEDI0680 (AMP-514)	Humanized IgG4	MedImmune/AstraZeneca	NCT02118337
	PDR001	Humanized IgG4	Novartis	NCT03066648
PD-L1	BMS-936559 (MDX-1105)	Human mAb	Bristol-Myers Squibb	NCT01452334
	Atezolizumab (RG7446 MPDL3280A)	Fully humanized IgG1	Genentech/Roche	NCT02862275, NCT02220842, NCT02892318
	Durvalumab (MEDI4736)	Fully human IgG1	MedImmune/AstraZeneca	NCT02733042, NCT02733042, NCT02685826, NCT02549651, NCT02807454, NCT02716805
	Avelumab (MSB0010718C)	Fully human IgG1	Pfizer/Merck	NCT02953561, NCT02603419

Table 7 *(continued)*

Table 7 *(continued)*

Target	Symbol	Type of drug	Developer	Select Phase I Studies in HM
CTLA-4	Ipilimumab (Yervoy)	Human IgG1	Bristol-Myers Squibb	NCT01896999
	Tremelimumab (CP-675)	Fully human IgG2	MedImmune/AstraZeneca	NCT02549651, NCT02716805
LAG-3	BMS-986016	mAb	Bristol-Myers Squibb	NCT02061761
	LAG-525	Humanized mAb	Novartis	N/A
	TSR-033	Antagonist mAb	TESARO	N/A
CD47	Hu5F9-G4	Humanized 5F9 mAb, IgG4	Forty Seven, Inc.	NCT02678338, NCT02953509
	TTI-621	SIRPαFc recombinant Fusion protein	Trillium Pharmaceuticals	NCT02663518, NCT02890368
	CC-90002	Anti-CD47, isotype unknown	Celgene	NCT02367196, NCT02641002
TIM-3	MBG453	mAb	Novartis	NCT02608268
	TSR-022	mAb	TESARO	N/A
KIR	Lirilumab (IPH2102/BMS986-015)	Fully humanized mAb	BMS/Innate Pharma	NCT02252263
	IPH2101	IgG4 mAb, anti-KIR (2DL1,2DL2, 2DL3)	BMS/Innate Pharma	NCT01217203
CD137/4-1BB	Urelumab	IgG4	Bristol-Myers Squibb	NCT02252263
	PF05082566	IgG2	Pfizer	NCT01307267
CD27	Varlilumab (CDX-1127)	Fully human IgG1 mAb	Celldex Therapeutics	NCT01460134
CD40	CP870,893 (RO700978)		Roche	N/A
	ADC-1013	Human IgG1	Alligator Bioscience AB	N/A
	SEA-CD40	Sugar-engineered non-fucosylated antibody	Seattle Genetics	NCT02376699
	APX005M	Humanized mAb	Apexigen	N/A
	Lucatumumab (HCD122)	Fully humanized mAb	Novartis	NCT00670592, NCT00231166, NCT00108108
GITR	MK-4166	Anti-human mAb	Merck	N/A
	TRX518	Humanized, Fc disabled mAb	Leap Therapeutics	N/A
	GWN323	Human IgG1	Novartis	NCT02740270
OX40	PF-04518600	Agonistic mAb	Pfizer	N/A
	RG7888 (MOXR0916)	Humanized mAb	Roche/Genentech	N/A
	MEDI6383	Human OX40 ligand fusion protein	MedImmune	N/A
IDO1	GDC-0919	Small molecule	Genentech	N/A
	Epacadostat (INCB024360)	Small molecule	Incyte	NCT02178722
	Indoximod	Small molecule	NewLink Genetics	NCT02835729

*, mechanism of action unclear after uncertainty as pidilizumab does not bind PD-1 (48). N/A, not applicable.

myeloid cancers. Ongoing attention to toxicity from immune-based approaches such as increased rates of GVHD in patients who go on to receive allogeneic stem cell transplantation after checkpoint blockade remains quite important. Clinical trials and detailed correlative studies evaluating T cell response, TME, and host factors will hopefully facilitate an understanding of how to gain durable disease control from immunotherapy while minimizing the risk of immune-related toxicities.

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Footnote

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