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Immune checkpoint blockade in hematological malignancies: current state and future potential

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Malignant cells are known to evade immune surveillance by engaging immune checkpoints which are negative regulators of the immune system. By restoring the T-lymphocyte mediated anti-tumor effect, immune checkpoint inhibitors (ICI) have revolutionized the treatment of solid tumors but have met rather modest success in hematological malignancies. Currently, the only FDA approved indications for ICI therapy are in classic hodgkin lymphoma and primary mediastinal B cell lymphoma. Multiple clinical trials have assessed ICI therapy alone and in combination with standard of care treatments in other lymphomas, plasma cell neoplasms and myeloid neoplasms but were noted to have limited efficacy. These trials mostly focused on PD-1/PDL-1 and CTLA-4 inhibitors. Recently, there has been an effort to target other T-lymphocyte checkpoints like LAG-3, TIM-3, TIGIT along with improving strategies of PD-1/PDL-1 and CTLA-4 inhibition. Drugs targeting the macrophage checkpoint, CD47, are also being tested. Long term safety and efficacy data from these ongoing studies are eagerly awaited. In this comprehensive review, we discuss the mechanism of immune checkpoint inhibitors, the key takeaways from the reported results of completed and ongoing studies of these therapies in the context of hematological malignancies.

KEYWORDS

immune checkpoint inhibitors, hematological malignancies, PD-1, CTLA-4, TIGIT, TIM-3, LAG-3, CD47

1 Introduction

Advances in cancer immunotherapy has significantly changed the treatment landscape for the treatment of hematological malignancies. The graft versus leukemia effect in the setting of allogeneic transplantation was the earliest demonstration of the potency of the immune system in targeting malignancy (1). A major area of research interest has focused on harnessing the power of the immune system to more specifically target the malignant clone, in an attempt to capitalize on the unique potency of immune mediating killing, while minimizing toxicity. A critical milestone in the history of cancer immunology was the

discovery of immune ‘checkpoints’, which act as negative regulators of effector T cells. Biologically, these immune checkpoints serve the important function of self-tolerance to avoid auto-immunity and are expressed on immunosuppressive regulatory T cells. Activation of these checkpoints result in decreased activation, proliferation, cytokine production and ultimately an apoptotic fate of the effector immune cells. Malignant cells hijack these negative regulators of the immune system to evade immune mediated killing. Inhibiting these immune check points with monoclonal antibodies has been shown to be a successful therapeutic strategy leading to significant improvement in the response and survival rates in certain malignancies. Despite revolutionizing the treatment landscape of multiple solid tumors including kidney cancer, melanoma and lung cancer, immune checkpoint inhibitors (ICI) have met mixed success in the treatment of hematological malignancies. Numerous PD-1 axis and CTLA-4 inhibitors are now commercially available and multiple other immune checkpoint targeting therapies are in development. This review will explore the various targetable immune checkpoint pathways and the status of their clinical application in the context of hematological malignancies.

2 Immune effector cells and their checkpoints

Antigenic stimulation of the T cell receptor (TCR), a clone specific cell surface complex, is a crucial step towards activation of the T cells (2). However, an additional co-stimulation step is required for T cell activation and proliferation. CD28 protein and its family members were noted to be potent co-stimulatory molecules for T cell activation (3, 4). CD28 ligands B7-1 (CD80) and B7-2 (CD86) are found on antigen presenting cells and binding of CD28 with B7-1/2 leads to activation of the co-stimulatory domain CD28.

Cytotoxic T lymphocyte associated antigen 4 (CTLA-4) is structurally similar but performs the opposite function to CD28. On binding to the same ligands, B7-1/2, expressed on the antigen presenting cells (APC). CTLA-4 causes inhibition of T cell activation primarily by interfering with the CD28-B7-1/2 interaction. Along with directly competing with CD28 for binding its ligands, it also internalizes the ligands leading to decreased binding with CD28 thereby decreased secretion of stimulatory cytokines like IL-2 and causes reduced T cell proliferation (5, 6). CTLA-4 also activates SHP2 and PP2A phosphatases which prevent phosphorylation of CD3 ζ an important part of the TCR complex (7). Presence of CTLA-4 on immunosuppressive regulatory T cells further confirmed its role as a negative regulator of the immune system. As such, inhibition of CTLA-4 to elicit a therapeutic immune response against cancer cells was a highly attractive proposition. This was successfully demonstrated by Allison et al. in 1996 in a mouse model. They showed that neutralizing anti-CTLA-4 antibodies lead to eradication of colon cancer and fibrosarcoma as well as induced anti-tumoral immunity (8). After demonstrating success in clinical studies, Ipilimumab was the first CTLA-4 monoclonal antibody to get FDA approval in 2011 (9).

The programmed cell death protein (PD)-1 was identified to play an analogous role to CTLA-4 and was noted to be expressed on

the T cells after TCR stimulation. On binding to its ligands PDL-1 (also known as B7-H1) and PDL-2 (B7-DC), it induces inhibitory intracellular signaling and inactivation of T cells (10). Similar to CTLA-4, PD-1 activates the SHP1 and SHP2 phosphatases which inactivate downstream signaling needed for T cell activation (11, 12). Contrary to regulation of early T cell activation in the lymphoid tissues by CTLA-4, the PD-1 axis is thought to play an important role in continued activation of T cells especially in the peripheral tissues and on engagement with the ligands, PD-1 induces a dysfunctional T cell state known as “T cell exhaustion” (13). Tumor cells use this negative regulator of the effector T cells by overexpressing PDL-1 or PDL-2. Subsequently this PD-1 axis was explored to be a therapeutic target to restore immune cell cytotoxicity against cancer cells. Monoclonal antibodies against PD-1 and PDL-1 have shown remarkable anti-tumor activity and have led to meaningful improvement in the clinical outcomes in various cancers.

Lymphocyte activation gene-3 (LAG-3, also known as CD223), another immune checkpoint, is a transmembrane protein expressed on the surface of both effector and regulatory T lymphocytes after antigen mediated stimulation (14). LAG-3 binds with stable complexed of peptide and MHC-II on the antigen presenting cells. Initial thought was that LAG-3 competitively inhibits CD4-MHCII binding but recently it was shown that LAG-3 suppressed T cells by transducing inhibitory signaling via in the intracellular domain (15). It is unclear if MHC II is the sole functional ligand of LAG-3. Fibrinogen-like protein 1 (FGL1) secreted by the liver is also implicated to be an immune-inhibitory ligand of LAG-3 particularly affecting CD8+ T cells. High levels of FGL-1 expressed by cancer cells are associated with poor prognosis (16, 17). Given its role in immune tolerance for cancer cells, LAG-3 blockade is being explored as a therapeutic target.

T cell immunoglobulin and mucin domain 3 (TIM-3) is an inhibitory immune checkpoint receptor frequently co-expressed with PD-1 on tumor infiltrating T cells as well as other innate immune cells like monocyte/macrophages, NK cells and dendritic cells. Galectin-9 (GAL-9) or carcinoembryonic antigen related cell adhesion molecule (CEACAM1) are known ligands of TIM3 which cause inhibitory signaling downstream causing T cell exhaustion or apoptosis (18, 19). TIM-3 signaling has been proposed as a resistance mechanism for PD-1 directed therapy due to the noted co-expression and therefore has been explored as a therapeutic target in many malignancies including hematological malignancies (20, 21).

T cell immunoglobulin and ITIM domain (TIGIT, also known as Vstm3, VSIG9, WUCAM) is another co-inhibitory transmembrane molecule exclusively expressed on T cells including CD4+, CD8+, regulatory T cells and NK cells. TIGIT activates a complex immunoregulatory network on binding with its multiple ligands including CD155, CD112, CD113 and Nectin-4 expressed by antigen presenting cells as well as cancer cells. The primary high affinity ligand for TIGIT is thought to be CD155 (22, 23).. Although not completely understood, TIGIT causes T cell inhibition by multiple mechanisms including TCR downregulation, competing for ligands with an activating co-receptor CD226 as well as enhancing the immunosuppressive effects of regulatory T cells.

Given its role in T cell inhibition and immune escape mechanism, TIGIT blockade has been explored as a therapeutic target in hematological malignancies (24). LAG-3, TIM-3 and TIGIT biology and its role for treatment of cancers has been reviewed in detail elsewhere (25, 26).

Macrophages are phagocytic cells and an integral part of the innate immune system. While these are traditionally thought to be functioning against infectious pathogens/foreign bodies, tumor associated macrophages were discovered to be involved in multiple malignancy processes like angiogenesis, metastasis, regulation of tumor microenvironment (27). CD47 is membrane protein first discovered to be present on erythrocyte surface. Senescent erythrocytes with diminished expression of CD47 are removed from circulation by macrophages in the spleen and liver (28). Normal erythroid cells are able to avoid this removal by expression of CD47 on their membrane which bind with macrophage inhibitory receptor signal regulatory protein alpha (SIRP α). This leads to downstream activation of SHP-1 and SHP-2 phosphatases causing phagocytic inhibition. Therefore, CD47 is commonly referred to as 'do not eat me' signal. Subsequently, it was discovered that CD47 is commonly over expressed on most tumor cells like AML, MDS, NHL as a macrophage checkpoint (29). Subsequently, CD47/SIRP α axis blockade was shown to effectively promote tumor cell phagocytosis as well as enhanced antigen presentation leading to a strong T cell mediated tumor response (30, 31). CD47 inhibition has progressed significantly in clinical investigation however a strong efficacy signal is yet to be noted.

3 Immune checkpoint blockade in lymphomas

3.1 Hodgkin lymphoma

Classic hodgkin lymphoma (cHL) has a unique biology. It is characterized by the malignant Hodgkin and Reed Sternberg (HRS) cells which comprise ~2% of tumor cells. The remaining tumor bed is primarily comprised of reactive T cells and immune cells. Studies have shown that these reactive immune cells have an exhausted phenotype leading to loss of effector function. This is due to overexpression of over-expression of PDL-1 and PDL-2 on the malignant HRS cells caused by amplification of the 9p24.1 locus (32). Treatment of cHL has evolved significantly over the years with combination chemotherapy as the backbone. Recently BV-AVD (Brentuximab vedotin, doxorubicin, vinblastine, dacarbazine) replaced ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) based on the improved survival with BV-AVD showed in the ECHELON-1 trial (33). Despite a large proportion of patients will achieve a complete response with frontline therapy, patients who have primary refractory or relapsed disease have poor outcomes. Salvage chemotherapy and high dose chemotherapy with autologous hematopoietic cell transplantation (auto-HCT) are used in this setting with significant treatment associated complications. Given the immunosuppressive biology of the HRS cells by overexpression of PDL-1/2, immune checkpoint blockade was first investigated in relapsed/refractory cHL. Checkmate-205 was a phase II trial that

studied nivolumab a monoclonal PD-1 antibody in 243 patients with relapsed/refractory cHL after failure of autoHCT. The overall response rate (ORR) was 69% with complete response (CR) in 16% patients. Median time to response was ~2 months and patients achieved response for a median duration of 16.6 months (34). Pembrolizumab another monoclonal PD-1 antibody was also studied in Keynote-087. In this study, 210 patients with relapsed refractory cHL who had previously received at least 2 lines of therapy including autoHCT and/or brentuximab vedotin were treated with pembrolizumab monotherapy until disease progression or unacceptable toxicity. The ORR was 72% with a CR rate of 28%. Similar to checkmate-205, median duration of response was 16.6 months. Another noteworthy finding from Keynote-087 was that among patients in CR who had discontinued pembrolizumab and subsequently had disease progression, 74% had an objective response lasting for a median of ~15 months (35). In both trials with nivolumab and pembrolizumab, patients who were BV naïve, had improved responses. Subsequently, a phase III randomized controlled trial (RCT), Keynote-204, comparing pembrolizumab and BV in the relapsed/refractory setting showed improved median progression free survival (PFS) with pembrolizumab (13.2 months) as compared to BV (8.3 months) (p 0.0027) Tolerance to pembrolizumab was better as compared to BV (36). Pembrolizumab in combination with chemotherapy regimen GVD and nivolumab with ICE have both shown impressive responses (ORR 100%, CR ~90%) as first salvage therapy for R/R cHL (37, 38). Based on these data, both pembrolizumab and nivolumab have been approved for the treatment of relapsed/refractory cHL. PD-1 blockade has also been studied as post autoHCT consolidation in high-risk patients with relapsed cHL with improved PFS although mature data is awaited at this time (39, 40). PDL-1 monoclonal antibody, Avelumab was studied in a phase 1 trial (JAVELIN Hodgkin) in patients with relapsed/refractory cHL which showed an ORR of ~42% with CR in 19.4% patients (41). Along with combination of chemotherapy and PD-1 blockade, studies have also evaluated the efficacy of a chemotherapy sparing salvage regimen of BV+PD-1 blockade in relapsed cHL. The ORR was 85% with a CR rate of 67%; these were durable responses with 3 year PFS ~77% (42). Given the resounding success of PD-1 blockade in the relapsed/refractory setting, there is excitement about the role of PD-1 blockade in combination with chemotherapy in the frontline setting. Results from the southwest oncology group (SWOG) 1826, a phase III trial comparing nivolumab-AVD Nivolumab (N)-AVD vs BV-AVD were presented at the 2023 ASCO meeting. With approximately 480 patients in both arms, the 1-year PFS rate was superior with N-AVD as compared to BV-AVD (94% vs 86%; HR 0.48; p=0.0005) with lower rates of adverse effects in the N-AVD arm (43). Full publication from this trial is eagerly awaited and has the potential to change standard frontline therapy for cHL. See Table 1 for key trials in hodgkin lymphoma.

Given the synergy that the combination of PD-1/CTLA-4 blockade has demonstrated in some solid tumors, including melanoma and renal cell carcinoma, this combination is being studied in cHL. In a phase 1/2 trial, patients with relapsed/refractory cHL were treated with either combination of BV and nivolumab or ipilimumab (CTLA-4 antibody) or both. This study demonstrated

TABLE 1 Key trials with Immune checkpoint inhibitors in Hodgkin lymphoma.

Trial	Phase	Intervention	Checkpoint target	Population	Efficacy	Adverse events (grade3-4) of checkpoint inhibitors
SWOG 1826 (NCT03907488)	III	Nivolumab-AVD vs Brentuximab vedotin (BV)-AVD	PD-1	Newly diagnosed advanced stage cHL (n=994)	1-year PFS: 94% vs 86% (HR 0.48; p=0.0005)	
CHECKMATE 205 (NCT02181738)	II	Nivolumab	PD-1	R/R cHL (n=243)	ORR 71% mPFS 15 months 5y OS 71%	Increased lipase (5%) Neutropenia (3%) Increased ALT (3%)
NCT02572167	I/II	Nivolumab+ BV	PD-1	R/R cHL (n=91)	ORR 85% 3-year PFS 77% 3-year OS 93%	Pneumonitis (3%) Rash (1%)
KEYNOTE 204	III	Pembrolizumab vs Brentuximab vedotin	PD-1	R/R cHL (n=304)	mPFS 13.2 vs 8.3 months (HR 0.65; p=0.0027)	Pneumonitis (4%) Neutropenia (2%)
KEYNOTE 087 (NCT02453594)	II	Pembrolizumab	PD-1	R/R cHL (n=210)	ORR 71% mPFS 13.7 months	Total 13% Neutropenia (2.4%) Pericarditis (1%) Diarrhea (1%)
JAVELIN Hodgkins (NCT02603419)	I	Avelumab	PDL-1	R/R cHL (n=31)	ORR 42% mDOR 6.9%	Rash (7%) Increased lipase (7%) Pneumonitis (3%) Immune thrombocytopenia (3%)

improved responses with BV+ nivolumab over BV+ ipilimumab or BV+ both groups. Unfortunately, about 43% patients in the BV+ipilimumab group suffered grade 3-4 adverse events. The phase 2 study comparing BV+ nivolumab with or without ipilimumab is ongoing (NCT01896999) (44).

One approach to overcome resistance to treatment with PD-1 inhibition is to combine PD-1 blockade with inhibitors of other checkpoints co-expressed on exhausted T cells, such as LAG-3. Favezelimab (MK-4280), a humanized IgG4 LAG-3 inhibitor, was studied in combination with pembrolizumab in patients with relapsed/refractory cHL. The combination demonstrated an ORR of 73% with an impressive CR rate of 30%. Median PFS was 19.4 months. Common adverse reactions included infusion reaction and hypothyroidism (immune related adverse event). 23% patients had grade 3-4 adverse reactions (45).

3.2 Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogenous group of malignant lymphoproliferative disorders classified according to the cell of origin into B cell NHL (>85%) and the less common T/NK cell NHL. Pre-clinical studies have shown that intratumoral CD4+CD25+ regulatory T cells suppress the infiltration of effector T cells in B cell NHL leading to immunosuppressive tumor microenvironment (46). These cells are enriched in negative immune regulators like CTLA-4 and therefore CTLA-4 blockade with ipilimumab was studied in a phase 1 trial for patients with relapsed/refractory B cell NHL. Unfortunately, of the 18 patients treated only 2 patients had clinical responses (11%) (47). Subsequently, ipilimumab in combination with rituximab in

patients with R/R B cell NHL showed a modest ORR of 24% with median PFS of 2.6 months (48). Combination of CTLA-4/PD-1 blockade with Ipilimumab/nivolumab showed ORR was 19% with median PFS of only 1 month (49).

PDL-1 expression on large B cell lymphoma cells was shown to have inferior outcomes mediated by suppression of anti-lymphoma immune response. As such, intercepting the PD-1/PDL-1 axis has been evaluated for clinical efficacy against R/R B cell NHL (50, 51). Multiple early phase studies showed safety but low efficacy of PD-1/PDL-1 blockade in R/R B cell NHL. In a multi-center phase 2 study of nivolumab in 121 patients with R/R DLBCL ineligible or refractory to autoHCT, the ORR was <10% (52). Similarly, in patients with R/R FL, the ORR of single agent nivolumab was a meager 4% (53). Another study in patients with FL (rituximab sensitive disease relapsed after >1 line of treatment), combination of pembrolizumab and rituximab had impressive ORR 67% with CR rate of 50%, however these were rituximab sensitive patients and it remains unclear if pembrolizumab had added benefit (54). A triplet combination of obinituzumab, lenalidomide and atezolizumab for patients with R/R FL showed an impressive CR rate of 72% with about 67% patients being refractory to rituximab and alkylator combination (55). However, durvalumab (anti PDL-1 antibody) in combination with Bruton Kinase inhibitor (BTKi) ibrutinib showed efficacy similar to single agent ibrutinib (ORR ~25%) in patients with R/R FL and DLBCL with added immune related toxicities (56). Addition of durvalumab to frontline R-CHOP in high risk DLBCL patients did not provide additional benefit (57). In patients with relapsed CLL or with Richter transformation (RT), pembrolizumab had a preferential efficacy in patients with RT (ORR 44%) while none in patients with CLL (58). Pembrolizumab in combination with dinaciclib (cyclin dependent kinase 9, CDK9 inhibitor) in

patients with R/R CLL, DLBCL and multiple myeloma (MM) showed a ORR of 20-30% in patients with CLL and DLBCL whereas 0% in patients with myeloma (59). Post autoHCT consolidation with pembrolizumab in DLBCL did not show improvement in PFS (60). Pembrolizumab has also been studied in the context of post CD19 CAR-T relapse. The response rate noted was 25%. Correlative studies showed that there was increase in the CAR-T cells by mass cytometry by time of flight and increase in CAR19 transgene levels in patients those responded to pembrolizumab (61).

In contrast to other B cell NHL, PD-1/PDL-1 blockade in primary mediastinal B cell lymphoma (PMBCL) has shown robust activity and is FDA approved. PMBCL is common in adolescents and young adults. Although it is morphologically similar to large B cell lymphoma, genomically, PMBCL is closer to cHL frequently involving alterations of 9p24.1 resulting in over-expression of PDL-1/2. Unsurprisingly, early studies with pembrolizumab in R/R PMBCL showed ORR of 41% with durable responses (62). The final analysis of Keynote 170 again showed ORR of 41% with CR rate of ~21%. 4-year PFS in all patients was 33%. Impressively, all patients achieving CR had durable responses without relapses after 4 years of follow up (63). In combination with brentuximab vedotin, nivolumab showed an impressive ORR of 70% with CR rate of 43% in patients with CD30 + R/R PMBCL with median duration of response not reached after about 11 months of follow up (64). Please see [Table 2](#) for key trials in non hodgkin lymphoma.

The mechanism of resistance to PD-1 axis blockade in NHL is unclear. Proposed mechanisms include low lymphocyte infiltration of the tumor, low MHC expression on tumor cells, presence of immunosuppressive cells and up-regulation of other immune checkpoint proteins (65, 66). Other T cell checkpoints (LAG-3, TIM-3, TIGIT) have been associated with lymphoma progression but clinical data on therapeutic targeting of these checkpoints are not available yet. LAG-3 inhibition in combination with PD-1 axis blockade is being studied in R/R lymphomas in an effort to overcome resistance to PD-1 directed monotherapy and results are awaited (NCT02061761). TIM-3 has been noted to be overexpressed via IL-12 which results in T cell exhaustion in FL, however clinical data regarding safety and efficacy is not available yet (67). Similarly, a pre-clinical model showing combination of PD-1 and TIGIT blockade having synergistic effect in eliminating lymphoma cells has been reported (68).

It has been demonstrated that CD47 expressing lymphomas have poor outcomes and frequently leads to extra nodal dissemination of the malignant lymphoma cells. Therefore, targeting of CD47 or the anti-phagocytic 'do not eat me' signal presents an exciting therapeutic opportunity to evoke macrophage mediated immune response augmented by rituximab (69–71). Magrolimab (Hu5F9-G4) is a first in class, humanized IgG4 monoclonal antibody targeting CD47. In a phase 1 study in 22 patients with R/R NHL, magrolimab in combination with rituximab, 50% patients had an ORR while 36% having a CR. At last follow up, 91% of the responses were ongoing (72). Another CD47 inhibitor, TTI-622, is being evaluated in combination with rituximab for treatment of R/R NHL with ORR of 20-30% (73, 74).

3.3 T/NK cell NHL

T/NK cell NHL, a rare subtype of NHL, is often associated with poorer prognosis compared to its B cell counterpart. Cutaneous T cell lymphomas (CTCL) (eg. Sezary syndrome, mycosis fungoides) are considered indolent whereas peripheral mature T cell lymphoma (PTCL) an all-inclusive term for the rest of T cell lymphomas usually are aggressive. These are typically treated with combination chemotherapy. However, these therapies are not curative, and most patients will relapse. Immune checkpoint therapies targeting CTLA-4, PD-1 axis cause activation of the T cells, therefore there is a theoretical concern for stimulating growth of T cell lymphomas leading to hyper-progression. Accordingly, in a study with nivolumab in R/R PTCL, 4 of the 12 patients treated had hyper-progressive disease and the responses achieved were short lived. The study was discontinued (75). However, in a multicenter phase 2 study of pembrolizumab in 24 patients with R/R CTCL, the ORR was 38% with durable responses (>50 weeks). A transient worsening of erythroderma and pruritis occurred in ~50% patients followed by improvement; however hyper progression was not noted (76). Another study with avelumab (anti PDL-1 antibody) in R/R extra-nodal NK/T cell lymphoma (ENKTL) showed ORR of 38% with CR in 24% patients. Although the non-responders showed early progression, responders continued to receive treatment and maintained response. High expression of tumor PDL-1 was associated with improved responses (77). These studies showed that the phenomenon of hyper-progression may not be directly associated with PD-1/PDL-1 blockade in T cell lymphomas. Intralesional injection of TTI-621, a macrophage checkpoint inhibitor (anti CD47 antibody), in patients with CTCL showed 34% responses (78). Systemic administration study of this agent is underway (73).

4 Immune checkpoint blockade in multiple myeloma

Multiple myeloma (MM) is a plasma cell neoplasm accounting for approximately 10% of all hematological malignancies. Significant advances in the field include development and implementation of immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), anti-CD38 monoclonal antibodies and anti-BCMA therapies including chimeric receptor antigen T cells (CAR-T) and T cell engaging bispecific antibodies (BsAb). However, despite these significant advances, patients ultimately develop a progressively resistant disease. Immune checkpoint blockade was evaluated in this setting supported by pre-clinical studies which showed overexpression of PDL-1 in myeloma cells and CTLA4+ regulatory T cells in the tumor microenvironment. PDL-1 expression has also been shown to increase the risk of progression from monoclonal gammopathy to multiple myeloma (79–81). Despite the strong pre-clinical rationale, most studies of immune checkpoint blockade in myeloma have been disappointing.

Pembrolizumab was studied in intermediate/high risk smoldering multiple myeloma (SMM). Of the 13 patients treated, only one patient

TABLE 2 Key trials with Immune checkpoint inhibitors in Non-Hodgkin lymphoma.

Trial	Phase	Intervention	Checkpoint target	Population	Efficacy	Adverse events (grade3-4) of checkpoint inhibitors
NCT02038933	II	Nivolumab	PD-1	R/R DLBCL (n=121)	ORR 10% mPFS 1.9 months mOS 12.2 months	Neutropenia (4%) Thrombocytopenia (3%) Increased lipase (3%)
CHECKMATE-140 NCT02038946	II	Nivolumab	PD-1	R/R FL (n=92)	ORR 4% mPFS 2.2 months	Diarrhea (2%) Neutropenia (2%) Pneumonitis (1%)
NCT03003520	II	Durvalumab with R-CHOP or R ² CHOP	PDL-1	Untreated high-risk DLBCL (n=46)	CR 54% PR 19%	
NCT02401048	I/II	Durvalumab with ibrutinib	PDL-1	R/R FL or DLBCL (n=61)	ORR 25% mPFS 4.6 months mOS 18.1 months	Neutropenia (21%) Rash (7%) Pneumonitis (3%)
NCT02332980	II	Pembrolizumab	PD-1	CLL with RT (n=9) or R/R CLL (n=16)	ORR 44% for CLL with RT ORR 0% for R/R CLL	Hematological toxicity (20%) Rash (4%)
KEYNOTE-170 NCT02576990	II	Pembrolizumab	PD-1	R/R PMBCL (n=53)	ORR 41.5% mPFS 4.3 months 4-year PFS 33% mOS 22.3 months 4-year OS 45.3%	Neutropenia (13%) Increased AST (2%)
CHECKMATE-436 NCT02581631	II	Nivolumab with brentuximab vedotin	PD-1	R/R PMBCL (n=30)	ORR 73% mPFS NR mOS NR	Neutropenia (7%) Rash (3%) Colitis (3%) Immune mediated hepatitis (3%)
CITN-10 NCT02243579	II	Pembrolizumab	PD-1	R/R CTCL (n=24)	ORR 38%	Rash (17%) Arthritis (4%) Pneumonitis (4%) Colitis (4%) Immune mediated hepatitis (4%)
NCT03075553	II	Nivolumab	PD-1	R/R PTCL (n=12)	ORR 33% mPFS 2.7 months mOS 6.7 months	Hyperprogression (33%)
NCT02953509	I	Hu5F9-G4	CD47	R/R NHL (n=22)	ORR 50% CR 36%	Infections (18%) Anemia (4.5%) Infusion reaction (4.5%)
NCT03530683	I	TTI-662	CD47	R/R lymphomas (n=42)	ORR 9/27	Thrombocytopenia (5%) Neutropenia (9%) Anemia (2%)

achieved a stringent CR with measurable residual disease (MRD) negativity while majority (85%) had stable disease. 3 patients discontinued treatment due to IRAEs (82). In a phase 1 study of pembrolizumab monotherapy for R/R MM, none of the 30 patients treated achieved an objective response. The best response achieved was stable disease with median duration of stable disease being 3.7 months (83). Nivolumab monotherapy in R/R MM patients lead to 4% objective response with majority (63%) achieving only stable disease (84). Safety profile of these agents in myeloma was congruent with

other cancers. After failure of PD-1 blockade monotherapy to demonstrate efficacy, combinatorial approaches were also evaluated. Combination of nivolumab with ipilimumab in a small subset of RRMM patients did not show any objective responses (85). Lenalidomide was shown to enhance efficacy of PD-1/PDL-1 blockade by inhibition of myeloid derived suppressor cells (MDSC) mediated immune suppression in addition to direct downregulation of PD-1 expression on T and NK cells providing a framework for clinical evaluation of this combination (86, 87). Keynote-023 was a phase 1

study which showed that combination of pembrolizumab and lenalidomide and dexamethasone had ORR of 76% in heavily pre-treated R/R MM patients including lenalidomide refractory cases (88). Pembrolizumab in combination with pomalidomide and dexamethasone had an ORR of 60% with median duration of response being 14.7 months (89). Keynote-183 was a phase 3 RCT evaluating pomalidomide and dexamethasone with or without pembrolizumab in a predominantly lenalidomide refractory population (86%). This study was stopped given the risk of triple combination outweighed the benefit. Median PFS was 5.6 months with the triple combination as compared to 8.4 months in the other arm and there were increased serious treatment related adverse events (69% vs 46%) with pembrolizumab. 3% treatment related deaths were reported in the pembrolizumab arm (90). Keynote-185 looked at lenalidomide and dexamethasone with or without pembrolizumab in transplant ineligible newly diagnosed multiple myeloma (NDMM). Unfortunately, this study was also halted due to a higher mortality signal in the pembrolizumab arm attributed to myocarditis, large intestinal perforation, pneumonia, pulmonary embolism etc. Serious adverse events were increased in the pembrolizumab arm as well (54% vs 39%) (91). Nivolumab in combination with pomalidomide and dexamethasone was planned to be studied in RR MM however, it was discontinued after interim analysis showed HR > 1 for PFS and OS in the nivolumab arm (92). Combination of PD-1/PDL-1 monoclonal antibodies with other active myeloma drugs including carfilzomib (proteasome inhibitor), daratumumab (anti CD38 mab) and elotuzumab (anti SLAMF7 mab) are also being tested. Atezolizumab in combination with daratumumab and lenalidomide/pomalidomide showed very good partial response or better in 50% patients (3/6) (93). Early results from nivolumab-daratumumab study showed an ORR of 50% for the combination in RRMM (94). PD-1 blockade has also been shown to enhance ex-vivo T cell response to autologous dendritic cell/myeloma fusion vaccine and is being studied clinically in clinical context (95). The biological rationale for the increased adverse effects and mortality with PD-1 axis inhibitors is not completely understood. Unfortunately, this has led to discontinuation of several clinical trials of PD-1/PDL-1 inhibitors in MM. Some of the major challenges of PD-1/PDL-1 inhibitors in MM relate to dysfunctional T cell phenotype having decreased effector capacity and immunosuppressive micro-

environment created by myeloid derived suppressor cells (MDSCs) and regulatory T cells. Despite the disappointing efficacy, patients achieving a response had a prolonged duration of response. Understanding the predictors of such responses would be key in optimizing patient selection for immune checkpoint therapy (96, 97). Please see Table 3 for key trials in multiple myeloma.

LAG-3 has been shown to be an important immune checkpoint in the pathogenesis and progression of myeloma. PD-1/LAG-3+ T cells are significantly enriched in patients with RRMM compared to NDMM (98, 99). Targeting the LAG-3/GAL-3 pathway has been shown to result in proliferation of MM specific T cells in combination with immunotherapy (100).

TIGIT has also been implicated in loss of myeloma specific immunity leading to disease progression. TIGIT blockade in combination with immunomodulators has been proposed as an exciting treatment modality to restore myeloma immunity (100). Exciting data from the MyCheckpoint study was recently presented at the AACR annual meeting. Anti TIGIT mab (BMS-986207) and anti LAG-3 mab (BMS-980616) were demonstrated to be safe alone and in combination with pomalidomide/dexamethasone. Objective response was noted in 2/6 patients treated with anti LAG-3 mab and in 3/6 patients treated with anti TIGIT mab (101). Longer follow up data is eagerly awaited.

TIM-3 is another checkpoint inhibitor proposed to play a role in T cell dysfunction and myeloma progression (102). TIM-3 pathway inhibition with anti-ligand antibodies led significantly higher NK cell cytolytic activity against myeloma cells and led to improved survival in a myeloma animal model (103). Clinical evaluation of TIM-3 inhibition in myeloma is warranted.

Myeloma cells have been shown to overexpress CD47 in a significantly larger amount compared to MGUS and SMM indicating a potential therapeutic target. Preclinical data has reported that CD47 blockade leads to induction of phagocytosis and killing of MM cells (104). Another correlative study of RRMM patients from the CoMMpass trial showed higher CD47 expression along with low CD38 expression correlated with worse overall survival and that dual inhibition of CD38 and CD47 had anti-tumor efficacy over single target inhibition (105). Clinical trials with CD47 inhibitors in myeloma area awaited.

TABLE 3 Key trials with Immune checkpoint inhibitors in plasma cell neoplasms.

Trial	Phase	Intervention	Checkpoint target	Population	Efficacy	Adverse events
CHECKMATE-039 (NCT01592370)	I	Nivolumab with ipilimumab	PD-1 and CTLA-4	R/R MM (n=5)	ORR 0%	29% grade 3-4 adverse events
KEYNOTE-013 (NCT01953692)	I	Pembrolizumab	PD-1	R/R MM (n=30)	ORR 0%	Myalgia (3%)
KEYNOTE-183 (NCT02576977)	III	Pembrolizumab with pomalidomide, dexamethasone vs pomalidomide, dexamethasone	PD-1	R/R MM (n=249)	mPFS 5.6 months vs 8.4 months	Serious adverse events 63% vs 46% Treatment related death 3% vs 0%
KEYNOTE-185	III	Pembrolizumab with lenalidomide, dexamethasone vs lenalidomide, dexamethasone	PD-1	NDMM (n=301)	6 month PFS 82% vs 85%	Serious adverse events 54% vs 39% Treatment related deaths 4% vs 1%

5 Immune checkpoint blockade in myeloid malignancies

Immunotherapy in the form of allogeneic hematopoietic stem cell transplant (allo-HSCT) has been a pillar in the management of myeloid malignancies. For the treatment of most types of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), allo-HSCT is the only known curative option. Because of the remarkable success of allo-HSCT in myeloid malignancies, there has been great interest in evaluating the therapeutic potential of other immunotherapies such as checkpoint inhibitors. Several trials have evaluated the efficacy of targeting pathways involving CTLA-4, PD-1, TIM-3 and CD47 in both AML and MDS.

Initial studies explored the use of ipilimumab in relapsed/refractory (r/r) AML and MDS in context of relapse post allo-HSCT (106–109). In a phase I/Ib trial, responses were observed in 5 out of 12 patients with relapsed AML after allo-HCT (108). Interestingly, of the 5 patients achieving CR, 4 had extramedullary disease and 3 responses lasted more than one year. Treatment was well tolerated with no major irAEs and no evidence of >grade 3 GVHD. Responses were related to bone marrow infiltration of cytotoxic CD8+ T cells and decreased systemic Treg activation (108, 109). In another phase Ib trial, non-transplanted patients with MDS who had failed hypomethylating agent therapy were treated with single-agent ipilimumab (110). Clinical activity of ipilimumab in this cohort of patients was very limited with only 1 out of the 29 patients achieving a CR. Of note, patients in this study only tolerated ipilimumab at a dose of 3mg/kg in contrast to the patients in the post-transplant trial (108) who tolerated a dose of 10mg/kg. This difference in dosing could account for the lack of response in the MDS trial. Most recently, a trial evaluating the combination of ipilimumab with decitabine in patients with AML and MDS (before and after allo-HSCT) reported encouraging results (111). The trial included 54 patients and demonstrated an overall response of 52% in patients who had not undergone transplant and 20% in patients post allo-HSCT. Similar to previous trials, most responses occurred at an ipilimumab dose of 10mg/kg. Despite meaningful response rates in this population, responses were short-lived with a median duration of response of 4.46 months and 6.14 in transplant-naïve and post-transplant patients respectively. From a safety standpoint, 11/25 patients in the post-transplant cohort had irAEs with 2 severe GVHD cases. In the transplant-naïve cohort, 11/23 patients reported irAEs. From a mechanistic standpoint, a parallel study concluded that decitabine acts on leukemic cells while ipilimumab acts on infiltrating lymphocytes and responses are determined by tumor cell burden and by the frequency and phenotype of infiltrating lymphocytes (111, 112).

Several studies have explored the use of pembrolizumab or nivolumab in myeloid malignancies. Given the known immune effects of hypomethylating agents (HMAs), most of these trials explored the efficacy of combination therapy using HMAs with pembrolizumab or nivolumab.

In a multi-center phase 2 trial, pembrolizumab was combined with azacytidine in patients with newly diagnosed and R/R AML (113). For the entire cohort (29 evaluable patients out of 37) the objective response rate (ORR) was found to be 55%. Significantly,

for unfit patients with newly-diagnosed AML, the ORR was 94% with 47% of patients achieving a CR/CRi. In another study, patients with r/r AML were treated with pembrolizumab and decitabine (114). Although the number of patients was smaller (10 patients), the ORR was similar to the pembrolizumab/azacytidine study (113) at 60%. In general, initial studies indicate that the combination of pembrolizumab with HMAs is a safe option with meaningful clinical responses in patients with AML.

In another phase 2 study, Zeidner et al. evaluated the combination of pembrolizumab with high-dose cytarabine (HiDAC) (115). The hypothesis was that pembrolizumab would augment anti-leukemia T-cell responses and work synergistically with HiDAC. The study enrolled 37 patients and the ORR was 46% with a CR/CRi rate of 38%. Significantly, 50% of CR/CRi patients achieved MRD negativity. Grade ≥ 3 irAEs were not significant. Of note, the authors concluded that this combination of agents was most effective in patients who received this treatment as their first salvage regimen (106, 115).

The KEYNOTE-013 study assessed the single-agent activity of pembrolizumab in patients with MDS after HMA failure (116). Unfortunately, this study did not meet its primary endpoint since none of the patients achieved a CR or PR. Another phase 2 study evaluated the combination of azacytidine and pembrolizumab in MDS patients (117). This study included MDS patients that were either HMA-naïve or HMA failures. The ORR was 76% (CR rate of 18%) in HMA-naïve patients and 25% (CR rate of 5%) in HMA-failure patients. Consistent with previous data, pembrolizumab does not have meaningful clinical activity in MDS patients who have failed HMA therapy, but it is a promising option in patient who are HMA-naïve.

A phase 2 study evaluated the combination of nivolumab with azacytidine (118). The trial enrolled 70 patients and 45 had prior exposure to HMAs. The ORR was 33% with only 4 patients achieving a CR. irAEs were similar to other studies of CPIs in AML patients with 11% of patients reporting incidence of irAEs. Interestingly, correlative studies determined that CTLA-4 was upregulated in non-responders. As a result, another cohort was included in this trial which enrolled 31 AML patients treated with the triplet of nivolumab, ipilimumab and azacytidine (119). The ORR was 46% with a CR/CRi rate of 36%. The overall survival (OS) was 10.5 months compared to 4.6 months in the nivolumab/azacytidine cohort. Not surprisingly, the incidence of irAEs was increased in the triplet cohort with 25% of patients reporting irAEs.

Nivolumab has also been evaluated in the front-line setting in a phase 2 trial combining it with cytarabine and idarubicin in patients with newly-diagnosed AML and high-risk MDS (120). The CR rate was 78% with 79% of those patients achieving MRD negativity. Additionally, 19 patients were taken to allo-HCT. Grade 3-4 GVHD was noted in 5 patients. Interestingly, the OS was not significantly different between responders who were bridged to allo-HSCT and those that continued therapy with nivolumab. Authors postulated that this could indicate that the nivolumab was the potential ability to restore anti-leukemic immune surveillance and eradicate MRD. Immune dysregulation in myeloid malignancies is complex and a poorly understood subject (121). Blockade of PD-1 axis alone has poor efficacy which improves modestly in combination with

hypomethylating agents or chemotherapy (122). Decreased MHC expression and negative regulation of T cells by way of increased alternative checkpoint expression, low T cell to MDS/AML cell ratio is thought to contribute to resistance to treatment, therefore effective therapies for tumor debulking and combination checkpoint blockade need further evaluation (112).

TIM-3 has been found to be upregulated on the surface of leukemia stem cells (LSCs) and leukemic blasts (123, 124). In addition, its expression is upregulated in malignant cells and it has been correlated with a poor clinical prognosis (125). All these findings make TIM-3 an attractive target in AML. Sabatolimab is a monoclonal anti-TIM-3 monoclonal antibody that is currently under investigation for the treatment of AML and MDS. Initial studies evaluated the combination of sabatolimab with HMAs in unfit patients with high-risk MDS and newly diagnosed AML (126, 127). In the MDS cohort, ORR was 57% with a CR rate of 43%. In the AML cohort, ORR was 40% with a CR/CRi rate of 30%. Responses were more durable in the MDS cohort with a median DOR of 16.1 months and 1-year PFS of 51.9% compared to a median DOR of 12.6 months and a 1-year PFS of 27.9% in the AML cohort. Meaningfully, subgroup analysis in this trial revealed that the response rates were preserved in patient with adverse risk mutations such as TP53, RUNX1 and ASXL1. In the AML cohort, in patients with at least one adverse risk mutation, the ORR was 53.8% with a median DOR of 12.6 months. In the MDS cohort, the ORR in patients with a TP53 mutation was 71.4% with a median DOR of 21.5 (127). Based on these data, there is a clear potential therapeutic effect in the use of sabatolimab in the treatment of AML and MDS and as a result the STIMULUS clinical trial program has been developed to study sabatolimab-based regimens in AML and MDS. Results from these studies will hopefully provide significant evidence showing a meaningful clinical effect of TIM-3 inhibition in AML and MDS.

In AML and MDS cells, it has been shown that CD47 is upregulated, and its upregulation is correlated with a poor clinical prognosis (128). Magrolimab is a humanized anti-CD47 monoclonal antibody that has been shown to induce macrophage-mediated phagocytosis of AML cells in preclinical studies (129). In clinical studies, it has been investigated as a single agent and in combination with HMAs for the treatment of AML. As a single agent, the responses were modest at best. In a phase I trial of single agent magrolimab in 15 r/r AML patients no CRs were achieved (130). Trials of the combination of magrolimab with azacytidine in AML and MDS showed more promising results (131, 132). In newly diagnosed, unfit AML patients, the ORR was 65% with a CR/CRi rate of 56%. In AML patients with a TP53 mutation, the ORR rate was 71% with a CR/CRi rate of 67%. In patients with untreated intermediate to very high risk MDS the ORR was 91% with a CR rate of 42%. These initial observations generated significant excitement in the field and several subsequent trials evaluating magrolimab in combinations with HMAs and/or venetoclax in patients with AML and MDS were initiated. Unfortunately, as of this writing the programs evaluating magrolimab in MDS have been halted due to futility and the programs evaluating magrolimab in AML are under a clinical

hold by the FDA. Please see Table 4 for key trials in myeloid neoplasms.

Another anti-CD47 antibody, evorpaccept, is currently under development. Evorpaccept is reported to have significantly lower rate of on-target, off-tumor toxicity when compared to magrolimab as it has an inactive Fc domain (133). Evorpaccept is being investigated in MDS and AML in the ASPEN clinical trial program. Results from these trials are eagerly awaited to provide further clarity regarding the therapeutic potential of CD47 blockade in AML and MDS.

6 Immune checkpoint blockade in the context of allogeneic HSCT

An important question in the field is whether the use of immune checkpoint inhibitors before or after an allogeneic transplantation improves outcomes, or whether this would result in an increase in toxicity due to GVHD. In initial studies, it was reported that Hodgkin lymphoma patients treated with an immune checkpoint inhibitor who subsequently underwent and allo-HSCT had an increased risk of complications including hyper-acute GVHD (134–136). Most recently, several studies have evaluated the use of immune checkpoint inhibitors before and after allo-HSCT in AML and MDS patients. Significantly, these studies have found no evidence of increased severe immune-related toxicities in AML/MDS patients treated with immune checkpoint inhibitors before or after allo-HSCT especially with the use of post-transplant cyclophosphamide as GVHD prophylaxis (120, 126, 137–140).

7 Toxicities of immune checkpoint blockade

Immune related adverse event (irAE) are a unique group of toxicities associated with immune checkpoint inhibitors. Different from toxicities of conventional cytotoxic chemotherapy, pathophysiology of these irAEs is not completely understood. Given the mechanism of action of checkpoint inhibitors, irAEs are thought to be mediated by increased T cell over activation and cytokine release (141, 142). These can be systemic adverse events presenting as fatigue or in severe forms cytokine release syndrome but more commonly are organ limited toxicities. irAEs commonly involve the skin, GI tract, thyroid, liver, and the lungs but can essentially involve any organ. The majority of the irAEs noted in clinical trials for hematological malignancies were mild to moderate and were able to be managed symptomatically or with corticosteroids. However, there are severe cases of irAEs presenting as pneumonitis, myocarditis, encephalitis, nephritis, Steven-Johnson syndrome etc. reported which led to death or significant comorbidity. Most of the data for irAEs specifically in hematological malignancies come from the early phase clinical trials as discussed previously. The two phase 3 studies including PD-1 inhibitor pembrolizumab in combination with immunomodulatory drugs in patients with multiple myeloma were Keynote-183 and

TABLE 4 Key trials with immune checkpoint inhibitors in myeloid neoplasms.

Trial	Phase	Intervention	Checkpoint target	Population	Efficacy	Adverse events (grade3-4)
NCT01822509	I	Ipilimumab	CTLA-4	Post AlloHCT relapse AML (n=12) MDS (n=2)	ORR 42%	IrAE 21% 14% GVHD
NCT02768792	I	Pembrolizumab	PD-1	R/R AML (n=37)	ORR 46% CRc 38% mOS 11.1 months	IrAE 14%
NCT03094637	II	Pembrolizumab	PD-1	HR MDS HMA naïve n=17 (Cohort A) HMA exposed n=20 (Cohort B)	Cohort A: ORR 76%, CR 18%. mOS NR Cohort B: ORR 25%, CR 5%. mOS 5.8 months	IrAE 43%
NCT02397720	II	Azacytidine with nivolumab with or without Ipilimumab	PD-1/CTLA-4	R/R AML Cohort 1: Aza+Nivo (n=70) Cohort 2: Aza+Nivo +ipi (n=31)	Cohort 1: ORR 33% Cohort 2: ORR 44% 1 year OS 45%	IrAE 25%
NCT02464657	II	Nivolumab with idarubicin+cytarabine	PD-1	Newly diagnosed AML/HR MDS (n=44)	ORR 77% mEFS not reached mOS 18.5 months	IrAE 14%
STIMULUS NCT03066648	I	Sabatolimab+HMA	TIM-3	Newly diagnosed HR MDS (n=53), AML (n=48)	MDS: ORR 57% mDOR 16 months AML: ORR 40% mDOR 12.6 months	IrAE 10%
ENHANCE NCT04313881	I	Magrolimab+HMA	CD47	R/R HR MDS (n=95)	ORR 75% CR 33% mDOR 9.8 months mOS NR	

Keynote-185. Both these studies were halted due to increased treatment related deaths in the pembrolizumab+IMiD arms related to severe IrAEs (myocarditis, pneumonitis, Steven Johnson Syndrome etc) (90, 91). Whether the toxicity was exacerbated in combination with an IMiD is a debatable question. In case of cHL, in the SWOG 1826 trial comparing Nivolumab-AVD to BV-AVD, Nivolumab-AVD was tolerated well and had a better safety profile compared to the control arm apart from hypo/hyperthyroidism which was manageable. There are multiple reviews discussing mechanisms and managements of checkpoint inhibition associated IrAEs in detail (142–144).

CD47 is critical to red blood cell homeostasis and targeting CD47 can potentially cause an ‘on-target off-tumor’ adverse effect of anemia. Therefore, an initial ‘priming’ dose of magrolimab (anti-CD47 mAb) has been proposed to assess anemia before proceeding to higher doses (145). Regardless of this strategy the most common magrolimab related adverse event is anemia (50-70%) (72, 145, 146).

8 Conclusion

Harnessing the potency of the immune system to target hematological malignancies has resulted in dramatic improvement in outcomes for patients with hematological malignancies. The discovery

of negative checkpoint pathways and their role in muting immune mediating targeting of tumor has been instrumental, and the development of immune checkpoint inhibitors has resulted in major therapeutic advances. While checkpoint blockers have shown efficacy in cHL and PMBCL, only limited efficacy was seen in non-Hodgkin lymphoma, plasma cell disorders and myeloid malignancies. There is significant room for improvement in development of immune checkpoint blockers in hematological malignancies. Efforts are underway to develop bispecific antibodies targeting two checkpoint molecules, checkpoint molecule and costimulatory molecule, checkpoint molecule and tumor target antigen etc. (147–151) Combination of checkpoint blockers with novel antibody drug conjugates are also a major area of research (152, 153). Most of these therapies are in the preclinical phase of development and data in the context of hematological malignancies is not available. Future directions will focus on understanding biomarkers predictive of response and resistance, on understanding the optimal timing for incorporating immune checkpoint blockade in the course of disease, and on developing novel combinatorial strategies.

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Conflict of interest

JV reports consulting scientific review committee with NexImmune, stock holding with NexImmune and speaker bureau with Kite/Gilead. JR reports consulting for Parexel, Bioclinica, Attivare. Serves on DSMB for Karyopharm. Advisory board for Janssen Research funding from BMS, Sanofi and Pfizer. In addition, JR has a patent for PCT/US2021059199 pending.

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