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Facts and Hopes in Immunotherapy of Lymphoma and Myeloma

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Abstract

Immune checkpoint blockade has driven a revolution in modern oncology, and robust drug development of immune checkpoint inhibitors is underway in both solid tumors and hematologic malignancies. High response rates to programmed cell death 1 (PD-1) blockade using nivolumab or pembrolizumab in classical Hodgkin lymphoma (cHL) and several variants of non-Hodgkin lymphoma (NHL) revealed an intrinsic biologic sensitivity to this approach, and work is ongoing exploring combinations with immune checkpoint inhibitors in both cHL and NHL. There are also preliminary data suggesting antitumor efficacy of PD-1 inhibitors used in combination with immunomodulatory drugs in multiple myeloma (MM), and effects of novel monoclonal antibody therapies on the tumor microenvironment may lead to synergy with checkpoint blockade. Although immune checkpoint inhibitors are generally well-tolerated, clinicians must use caution and remain vigilant when treating patients with these agents in order to identify immune related toxicities and prevent treatment-related morbidity and mortality. Autologous stem cell transplant is a useful tool for treatment of hematologic malignancies and has potential as a platform for use of immune checkpoint inhibitors. An important safety signal has emerged surrounding the risk of graft-versus-host-disease (GVHD) associated with use of PD-1 inhibitors before and after allogeneic stem cell transplant. We aim to discuss the facts known to date in the use of immune checkpoint inhibitors for patients with lymphoid malignancies, and discuss our hopes for expanding the benefits of immunotherapy to patients in the future.

Introduction

Blocking inhibitory surface receptor-ligand pairs, which function to limit T cell activation and autoimmunity has revealed a critical role for immune checkpoints in aiding cancer's evasion of host immunity (1–3). Blockade of immune checkpoints cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1) is revolutionizing treatment in many types of solid tumors by stimulating endogenous antitumor immune responses(4). Immune checkpoint blockade therapy (CBT) is also under development in several subtypes of hematologic malignancies, with impressive responses seen in relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) and recent promising results seen in

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multiple myeloma (MM) combining CBT with immunomodulatory drugs (IMiDs). Herein, we will review the development of CBT for the treatment of lymphoid cancers to date and discuss opportunities for future progress.

Immune checkpoint blockade in lymphoma

Hodgkin lymphoma can be cured in the majority of cases, however despite optimal therapy, salvage autologous stem cell transplant (auto-HSCT), and brentuximab vedotin (BV), additional treatment options are needed for a subset of relapsing patients. cHL is characterized by the presence of an inflammatory immune infiltrate surrounding the malignant Hodgkin Reed Sternberg (HRS) cell and near universal genetic amplification of the 9p24.1 locus that encodes the PD-1 ligands as well as *JAK2*, which in a dose-dependent fashion can further upregulate *PD-L1* expression via JAK2-STAT signaling(5). These observations formed the rationale for exploring CBT in this patient population. Patients with cHL treated with anti-PD-1 experienced objective response rates that were higher than expected, suggesting a potential intrinsic sensitivity to PD-1 blockade directly correlated with the degree of 9p24.1 amplification(5–11).

Patients with R/R cHL after auto-HSCT and BV receiving nivolumab on the phase I CheckMate039 study(7) had an 87% overall response rate (ORR), with 17% reaching a complete response (CR) and 70% achieving partial response (PR). The phase II CheckMate205 study (9) demonstrated an overall response rate of 66%, with 7 reaching CR, and 26 patients reaching PR. The phase I study of pembrolizumab (KEYNOTE-013) showed an ORR of 58%, CRR of 19%, and 12% of patients reached PR(12,13). In the phase II study (KEYNOTE-087) exploring pembrolizumab among three cohorts defined by history of auto-HSCT and exposure to BV, there was an ORR of 65.4–68.3%, CRR of 21.7–20%, and 93.7% of patients had a reduction in their tumor burden by radiographic assessment(14). In patients with R/R cHL after auto-HSCT and BV, the landmark clinical trials of immune checkpoint blockade led to accelerated approval of nivolumab and pembrolizumab by the Food and Drug Administration (FDA) for this indication.

Beyond its use in relapsed/refractory patients, PD-1 pathway blockade in combination therapies are being rapidly explored in other cHL populations, including newly diagnosed patients, autologous transplant in the salvage setting, transplant-ineligible patients, brentuximab-naïve patients, and patients with localized early stage disease with unfavorable characteristics. (Table 1). Early data is encouraging. Interim results from the phase I/II study of nivolumab combined with brentuximab vedotin as first salvage therapy after frontline chemotherapy before auto-HSCT showed a complete response rate (CRR) of 63% among the 59 evaluable patients, a rate significantly higher than expected with use of either agent alone(15). In R/R cHL, early data from the phase I ECOG-ACRIN E4412 study presented recently showed a CRR of 61% in 18 evaluable patients among 19 treated with the combination of nivolumab plus one of two dose levels of brentuximab vedotin (n=10 with1.2 mg/kg and n=9 with 1.8 mg/kg)(16). In the brentuximab plus ipilimumab arms, patients treated with brentuximab vedotin 1.8 mg/kg plus one of two dose levels of ipilimumab (1mg/kg or 3mg/kg) responded at a rate of 67%, with 5/12 (42%) achieving CR, with responses seen at both dose levels(17). Brentuximab vedotin plus nivolumab will be further

evaluated in a pending phase III clinical trial in auto-HSCT-ineligible or R/R patients (CheckMate 812, NCT03138499).

Among the non-Hodgkin lymphomas (NHL), PDL1 overexpression is observed in many entities, including primary mediastinal large B-cell lymphoma (PMBL), primary CNS lymphoma, primary testicular lymphoma, plasmablastic lymphoma, HHV-8 associated primary effusion lymphoma, T-cell/histiocyte-rich B-cell lymphoma, both Epstein Barr Virus (EBV) -positive and EBV-negative post-transplant lymphoproliferative disorders and EBV-associated diffuse large B cell lymphoma and extranodal NK/T cell lymphoma (ENKL) (18,19). Some NHL subtypes, such as PMBL, derive PDL1 overexpression from 9p24.1 mutations or copy number alterations. (5,19). In other entities EBV drives PD-L1 overexpression through a mechanism independent of 9p24.1 amplification through effects of the EBV-encoded latent membrane protein-1 (LMP-1) which promotes *AP1* and *JAK-STAT* signaling and increases PD-L1 expression via an AP-1 dependent enhancer (Figure 1)(19–21). Recent studies have focused on entities with PDL1 expression and promising activity was observed in the phase Ib study with PMBL (ORR 41% among 17 patients) as well as a phase II study in mycosis fungoides/Sézary syndrome (ORR 38% among 24 patients) (10,22,23). In addition, impressive activity was reported in small retrospective series of patients with ENKL and CNS lymphoma(20,21). Building upon this data, a prospective study in CNS lymphoma is underway (clinicaltrials.gov NCT02857426) and further analysis in ENKL is certainly warranted. Apart from PD-1, markers of immune exhaustion LAG-3 and TIM-3 are co-expressed in T cell infiltrates in NHL and represent potential additional targets for checkpoint blockade with *in vitro* data supporting this approach(24,25).

Despite remarkable activity of anti-PD-1 in cHL and several variants of NHL, a subset of patients experience progressive disease after an initial response, or are primary refractory to PD-1 blockade underscoring the importance of elucidating mechanisms of response and resistance beyond 9p24.1 amplification. Studies from solid tumors highlight a need for tumor cell recognition by T cells for efficacy of CBT, a process that requires relevant antigens and antigen presentation machinery(26). A retrospective series found decreased or absent expression of β2M and/or MHC I in 80% and decreased or absent MHC class II in 70% of cHL patients; β2M is the most frequently mutated gene in cHL(27). A retrospective analysis of 108 newly diagnosed cHL patients treated with conventional chemotherapy plus modified involved field radiotherapy found that those with reduced or absent β2M or MHC class I expression on HRS cells had poor outcomes independent of 9p24.1 status(28). Loss of MHC-II expression on HRS cells is also found more commonly in patients with relapsed cHL compared with newly diagnosed patients(29). Although the relationship between β2M mutations and response to CBT has not yet been described in cHL, β2M mutations and loss of MHC-I in melanoma have been described in patients with progressive disease and resistance to PD-1 blockade(30). Identification of tumor antigens in cHL is complicated by the relative rarity of HRS cells in the tumor microenvironment and requires enrichment techniques such as laser-capture microdissection or cell-sorting using flow cytometry(27). As such associations between antigen specific immune response against either shared or mutation-derived neo-antigens and efficacy of PD-1 blockade are not known. Additional research is needed to better define mechanisms of resistance to PD-1 blockade in cHL in

order to inform design of rational clinical trials aimed toward achieving durable remissions in a larger proportion of patients.

Immunotherapy for multiple myeloma: combinations offer a path forward

Preclinical data support a role for the PD-1/PDL1 pathway in myeloma via expression of the PD-1 receptor on T and NK cells in patients with MM and expression of PD-1 ligands on malignant plasma cells(31). T cells have been shown to recognize abnormal plasma cells (PC), as supported by detection of marrow-infiltrating T cells in MGUS capable of mounting anti-PC immune responses and presence of immunity against shared antigens is associated with prolonged progression to over symptomatic MM. However, once symptomatic MM develops, marrow T cell responses have not been observed without *ex vivo* expansion steps(32–34). The reasons for the loss of antigen-specific T cell activity *in vivo* in MM compared with precursor disease is not well understood, but could be due to progressive immunosuppression by the tumor microenvironment during disease progression from MGUS to MM, in contrast to the pro-inflammatory milieu present in the cHL tumor microenvironment (Figure 1). Perhaps the relative paucity of antigen-specific T cells is one reason that anti-PD-1 monotherapy using nivolumab had limited clinical activity(10). Interestingly, lenalidomide administration appeared to have transient efficacy immediately following nivolumab during a period of where prolonged receptor occupancy of the PD-1 receptor was expected(35).

IMiD drugs (thalidomide, lenalidomide, and pomalidomide) enhance T cell responsiveness to APC and polarize T cells toward a Th1 phenotype, inhibit myeloid derived suppressor cells (MDSC) and regulatory T cells (Treg), and down-regulate PD-L1 on tumor cells (36–39). These observations suggested the hypothesis that IMiD and PD-1 blockade combinations could result in clinically relevant antimyeloma immune responses in relapsed, refractory MM (Table 2). The KEYNOTE-023 study evaluating pembrolizumab, lenalidomide, and dexamethasone demonstrated an ORR of 44% (n=50), with sCR 4%, VGPR 12%, and PR of 28%. Lenalidomide-refractory patients responded to pembrolizumab plus lenalidomide and dexamethasone at a rate of 35%, with 5.4% achieving sCR, 8.1% reaching VGPR, and 21.6% achieving a PR(40). A phase II study of pembrolizumab, pomalidomide, and dexamethasone demonstrated an overall response rate of 60% (29/48), with 4(8%) reaching sCR/CR, 9(19%) reaching VGPR, and 16 (33%) reaching PR. Although limited by a small sample size, correlative analyses of pre-treatment tissue biopsies demonstrated that presence of CD3+/PD-1+ marrow-infiltrating lymphocytes was associated with shorter progression free survival(41). Patients expressing PD-L1 in the bone marrow before treatment had a trend toward a higher rate of responses of VGPR or better(41). An alternative hypothesis for the failure of PD-1 monotherapy in MM proposes that clonal bone marrow T cells expressing PD-1 in MM exhibit a telomere-independent senescence phenotype and are unable to respond to reinvigoration with immune checkpoint blockade(42). Additional biomarker studies are needed to better understand the association between response and PDL1 expression in MM marrow; and if PD-1+ T cells in MM are senescent T cells or can be re-invigorated (43).

Additional combination strategies in MM: shifting the balance in the microenvironment

Encouraging clinical activity observed with the IMiDs and anti-PD-1 combinations has spurred evaluation of agents capable of shifting the tumor microenvironment toward immune activation while inducing myeloma cell killing. In this regard, CD38 has emerged as an interesting target in MM due to high-levels of expression on plasma cells, a contribution to T cell anergy through ectoenzyme function that leads to adenosine production and expression on inhibitory cell populations such as MDSC and Treg (44,45). Targeting CD38 with daratumumab kills malignant plasma cells through traditional antibody dependent cellular cytotoxic (ADCC) mechanisms. In responding patients, daratumumab also appears to not only deplete subpopulations of Treg and MDSC in the myeloma microenvironment, but also result in T cell expansion and increased T cell clonality suggestive of an immune mechanism of myeloma disease control (46). These observations have provided rationale for investigation of daratumumab in combination with PD-1/PDL1 blockade with or without IMiD drugs (NCT01592370, NCT03000452, NCT02431208).

Radiation may also be an effective combination partner with PD-1 blockade by taking advantage of *in situ* vaccination caused by immunogenic cell death. Radiation has been shown to result in epitope spreading and augmented antigen-presentation by local APC. These effects have been associated with abscopal (distant) clinical effects in a variety of diseases (47–49). Temporal upregulation of PDL1 in the irradiated tumor suggests intrinsic mechanisms that inhibit immune responses after radiation, and provides rationale for blockade of PDL1 in combination with radiation(50) to overcome this mechanism. Several reported cases of systemic responses in patients with MM and plasmacytomas irradiated while receiving anti-PD-1 suggest potential induction of abscopal effects (41,51), which previously have been reported to occur spontaneously in very rare instances (52–54). We have recently begun enrollment of a combination trial using radiation plus PD-1 pathway blockade in patients with solitary bone plasmacytoma and limited clonal bone marrow plasmacytosis (NCT03196401) with the aim to elicit systemic immunity and the abscopal effect.

Hematopoietic Cell Transplantation: Risks, Rewards, and Potential

Both autologous and allogeneic HSCT are commonly used for treatment of patients with hematologic malignancies. In addition to antitumor responses produced by immunological graft versus tumor (GVT) effects after allo-HSCT, immune responses by the donor immune system against non-tumor host tissue can result in acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD), leading to morbidity and treatment-related mortality (TRM). The normal function of immune checkpoints limit T-cell mediated immune responses against host tissues. Relapse after allo-HSCT represents a significant clinical dilemma and CBT is also being explored in this patient population. Preclinical studies examining PD-1 axis blockade after allo-HSCT demonstrated not only potentiation of GVT effects(55,56), but also evidence supporting exacerbation of GVHD(57).

The feasibility of immune checkpoint inhibition for treatment of hematologic cancers relapsing after allo-HSCT was first explored using CTLA-4 blockade with ipilimumab in two studies with responses observed in both lymphoid and myeloid malignancies without high rates of treatment-emergent GVHD(58,59). Several series further elaborate on efficacy and toxicity of PD-1 inhibitor use before or after allo-HSCT (Table 3). Based on early reports suggesting a toxicity signal of hyperacute, severe acute and chronic GVHD, and 4 treatment-related deaths observed among 39 patients who received PD-1 blockade before allo-HSCT (60), a warning was added to the FDA package insert for nivolumab(61). The FDA recommends that patients receiving allo-HSCT after PD-1 blockade be closely monitored for early evidence of transplant-related complications, such as hyperacute GVHD, severe acute GVHD, steroid-requiring febrile syndrome (as a potential harbinger of severe acute GVHD), hepatic veno-occlusive disease, and other immune mediated reactions.

For patients with relapsed cHL after allo-HSCT, limited treatment options have led to increased off-label usage of PD-1 inhibitors. These data suggest that patients can achieve objective responses to PD-1 blockade after allo-HSCT (ORR: 77–95%), but this is complicated by a significant risk of developing severe treatment-emergent GVHD in up to 30–55% of patients. Among 53 total patients with publicly reported outcomes following receipt of PD-1 inhibitors after allo-HSCT, the observed rate of treatment-emergent GVHD was 47.2%, with 30.2% of treated patients developing grade 3–4 acute or severe chronic GVHD (62–64).

Given the potential risk involved with the use of PD-1 inhibitors before or after allogeneic stem cell transplant, this approach should only be pursued in the context of a clinical trial. PD-1 blockade is being formally explored in prospective studies after allo-HSCT as maintenance therapy (NCT02985554). Perhaps these studies will provide greater insight into predictors of GVH risk versus GVT benefit of this approach and define appropriate patient populations in which clinicians can safely harness the potential of PD-1 blockade to maintain a meaningful GVT response while minimizing the risk of developing treatment-emergent GVHD after CBT.

Auto-HSCT avoids the challenges of GVHD, but absence of GVT is thought to be a limitation to durability of responses. Nevertheless, the dynamics of immune reconstitution early after autologous stem cell transplant alter the immune regulatory network to favor autologous graft versus tumor response that may be further augmented by immune checkpoint inhibition(65). For example, Treg populations decline as CD8+ T cells expand during early lymphocyte recovery after autologous stem cell transplant. Seeking to harness this potentially favorable immune phenotype, a trial testing autologous lymphocyte infusions and combined CTLA-4 and PD-1 pathway blockade in concert with auto-HSCT for MM is ongoing (NCT02716805). In addition, recent studies showing that T cells produced by the autograft are able to respond to APC and develop into antigen-specific CTLs as early as 12 days after auto-HSCT support vaccine strategies in this setting as well(65). Several ongoing studies aiming to improve durability of disease control following auto-HSCT via induction of MM-directed immune responses include a DC-tumor cell fusion vaccine (NCT02728102), a WT1-directed vaccine (NCT01827137), and an RNA-electroporated DC

vaccine (NCT01995708). Future combinations trials incorporating vaccines with CBT in the post-autologous transplant space are a logical extension of these studies.

Immune-related toxicities of checkpoint blockade in hematologic malignancies

Immune checkpoint blockade is well tolerated in many patients, but immune mediated toxicities do develop. Three phase I studies in hematologic malignancy trials reported a drug-related grade 3 adverse event (AE) rate ranging from 18–20%, a small number of grade 4, and a single case of fatal pneumonitis (7,10,12).

The phase II studies of pembrolizumab and nivolumab in R/R cHL demonstrated acceptable safety profiles consistent with prior PD-1 inhibitor phase I studies. In the phase II study of nivolumab, 13/210 (5.4%) of patients had a treatment-related grade 3 AE, and there were no treatment-related grade 4 or 5 AEs reported. In the phase II study of pembrolizumab 22/80 patients had grade 3 AEs by investigator assessment, 2 patients had grade 4 increased lipase and one patient developed grade 4 neutropenia and there were no reported treatment related deaths(9,14).

In MM, pembrolizumab plus pomalidomide and dexamethasone did not appear to result in additive toxicity greater than that seen in solid tumors(66). Six patients developed immune mediated pneumonitis, the majority of which were grade 1–2 in severity, only one patient developed grade 3 pneumonitis(41), despite pomalidomide's association with pneumonitis (67). Of note, a hold on accrual of subjects to the phase III KEYNOTE-183 and KEYNOTE-185 studies evaluating the additive benefit of pembrolizumab to lenalidomide and dexamethasone or pomalidomide and dexamethasone was instituted by Merck in June 2017 due to excess deaths in the pembrolizumab treatment arm. Further evaluation of this safety signal is pending. In our experience, early detection and treatment of immune-related AEs is critical as the severity of an these events seems to be inversely proportional to the time from onset of symptoms to treatment. As clinicians become accustomed to the patterns of toxicities seen with CBT, it is expected the severity of toxicities should diminish.

Future Directions and Conclusions

Clinical successes with blockade of the PD-1 pathway in cHL have lead to regulatory approvals and significant excitement among clinicians in evaluating the utility of these treatments earlier in disease natural history. Genetically driven increases in the 9p24.1 locus in HRS cells appear to have a clear association with depth of response underscoring an intrinsic sensitivity to PD-1 blockade in cHL. However, absence of antigen presentation machinery in most HRS cells highlights that additional study is needed to understand precise mechanisms of activity of PD-1 blockade in this disease. A broad range of combination trials currently ongoing will undoubtedly define how to best use PD-1 blockade within the landscape of cHL therapy over the coming years. It is hoped that further study of mechanisms of activity in cHL will enable tailoring of better patient selection for specific combination approaches and perhaps addressing emergent resistance. Beyond cHL, PD1 blockade is active in several virally-driven NHL subtypes and entities with 9p24.1

abnormalities; prospective clinical studies of immune checkpoint inhibitors are ongoing to follow up these observations. In subtypes of lymphoma with limited response to checkpoint blockade, development of reliable biomarkers to predict which subsets of patients might respond to these agents are needed.

In contrast, single agent PD-1 pathway blockade in MM was underwhelming. Fortunately, rationally designed combination trials with IMiDs in MM have had encouraging results and opened the door to pivotal phase III trials whose results are eagerly awaited. Additional immunotherapeutic interventions in MM, including monoclonal antibody therapy with daratumumab or elotuzumab, vaccine strategies and highly encouraging early data from chimeric antigen receptor modified T cell therapies form unique opportunities to rapidly evaluate rational combination strategies.

Numerous additional questions remain on the use of immune checkpoint blockade therapy in these two distinct diseases. Can stem cell transplant, radiation, and other chemotherapies routinely used in cHL and MM combinations result in a favorable efficacy/safety profile? Will evaluating PDL1 expression, T cell clonality, or other biomarkers derived from studies in solid tumor malignancies have applicability in cHL, MM, and other lymphoid malignancies? What is the role of antigen specific immunity in these diseases in the context of checkpoint blockade and will shared or neo-antigens emerge as potential predictors of activity? Are there additional immune checkpoints or agonists whose modulation will also be therapeutically effective for these diseases? The emerging paradigm has been to evaluate combinations on a PD-1 blockade backbone, but perhaps this approach will mask unique biology or augment toxicity of other immune modulatory pathways.

Partnership of immune checkpoint antibodies with other immune-based approaches such as adoptive cellular immunotherapy such as chimeric antigen receptor modified T (CAR-T) cells or antibody engineering products such as bispecific T cell engagers (BiTEs) might exhibit synergistic activity. Vaccine-based approaches aimed at stimulating antigen-specific immunity to shared tumor antigens or neoantigens potentially through dendritic cell based platforms could also be rationally combined with immune checkpoint blockade to amplify antitumor immune responses.

Tumor immunotherapy originated more than 120 years ago by William Coley and his induction of inflammation by direct tumor inoculation of bacterial products at the turn of the 20^{th} century. Years of basic science investigations since that time have delineated pathways of immune activation and regulation; and ultimately have yielded the realization that negative regulators of immune activation are dominant pathways of cancer immune evasion. As such, checkpoint blockade has in effect re-invigorated the entire field of tumor immunotherapy.

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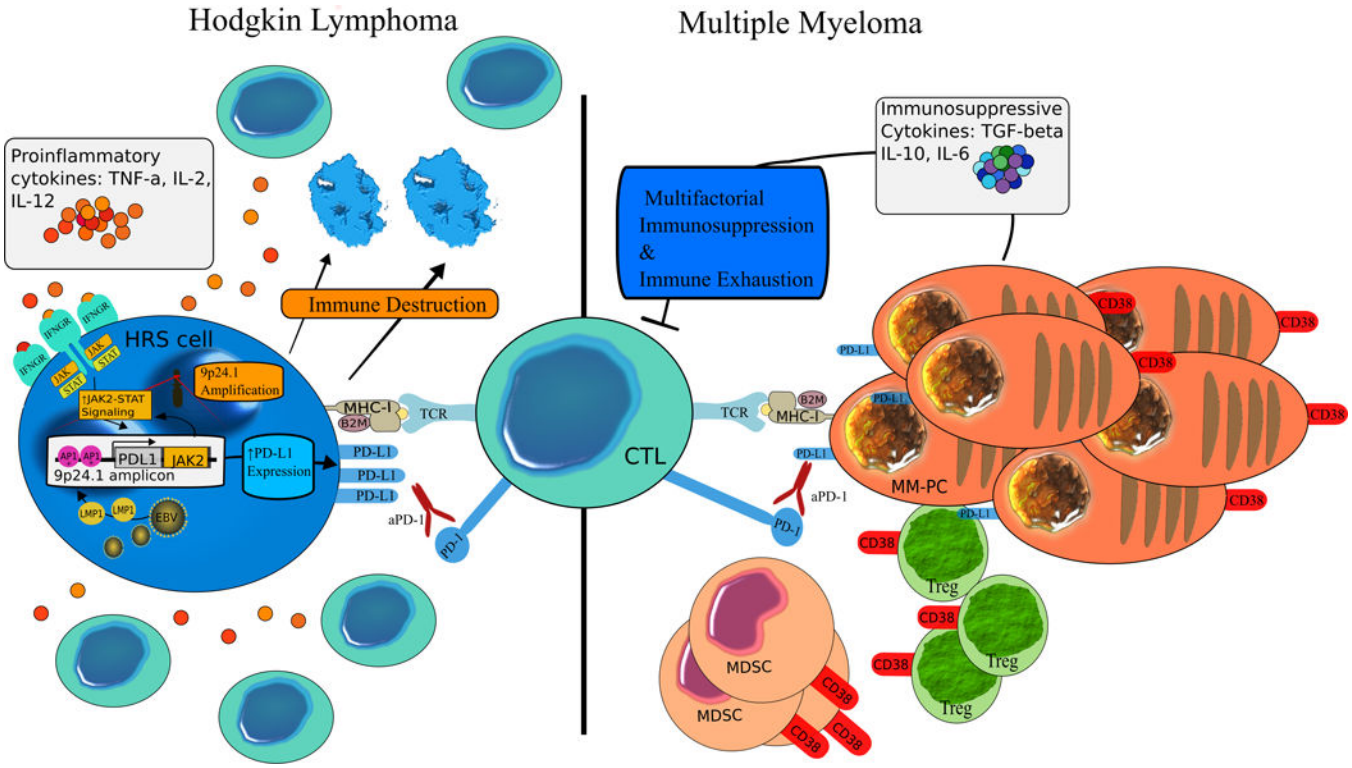

Figure 1.

Comparing the immune microenvironment in Hodgkin lymphoma and multiple myeloma. AP-1 = activating protein-1, B2m = beta-2 microglobulin, CTL = cytotoxic T lymphocyte, EBV = Epstein Barr Virus, IFNGR = Interferon gamma receptor, IL-2 = Interleukin 2, IL-12: Interleukin 12, IL-10: Interleukin-10, IL-6: Interleukin 6, HRS = Hodgkin Reed Sternberg Cell, JAK2 = Janus Kinase 2, AP1, LMP1 = Latent membrane protein-1PD-1= Programmed cell death 1, PD-L1 = Programmed cell death ligand 1, MDSC = Myeloid-derived suppressor cells, aPD-1 = anti-PD-1, MM-PC = Multiple Myeloma clonal plasma cell, TCR = T cell receptor, TGFb = transforming growth factor beta, TNF-a = tumor necrosis factor alpha. Treg = regulatory T cell, MHC-I = major histocompatibility complex I, MHC-II major histocompatibility complex II.

Table 1

Upcoming studies of immune checkpoint blockade in cHL

Disease Setting	Regimen	Target	Phase	Status	Est. Study Completion Date	NCT
Newly Diagnosed, untreated cHL						
Newly diagnosed cHL (age <60 with HR features, age >60)	A(B)VD +Nivo	PD-1	I	Recruiting	01/2020	NCT03033914
Early stage, unfavorable risk, no prior treatment.	Nivo + AVD -> IFRT vs. Nivo × 4 cycles -> Nivo + AVD × 2 cycles -> AVD × 2 cycles -> IFRT	PD-1	II	Recruiting	12/2020	NCT03004833
Age>60, ineligible for or declined conventional chemotherapy	Nivo + BV vs BV + Benda vs. BV + dacarbazine vs BV	PD-1	II	Recruiting	10/2018	NCT01716806
Untreated, transplant ineligible	Nivo + BV	PD-1	II	Recruiting	05/2024	NCT02758717
Relapsed/Refractory cHL						
Early stage Relapsed or Primary Refractory cHL	Pembro + ISRT	PD-1	II	Recruiting	06/2020	NCT03179917
R/R cHL (No prior BV, IO agent, or transplant)	Nivo + BV	PD-1	I/II	Recruiting	05/2020	NCT02572167
R/R cHL (2nd line only)	Nivo + ICE	PD-1	II	Recruiting	04/2019	NCT03016871
R/R cHL, no prior SCT (allo or auto)	Pembro + ICE	PD-1	II	Recruiting	02/2020	NCT03077828
R/R cHL, prior auto or allo HSCT allowed, BV, and IO agent allowed	Ipi + Nivo + BV vs Ipi + BV vs. Ipi + Nivo + BV	CTLA-4, PD-1	I	Recruiting	06/2018	NCT01896999
R/R cHL (no prior allo-HSCT)	Avelumab	PDL1	Ib	Recruiting	09/2017	NCT02603419
R/R cHL (no prior allo-HSCT)	Ibrutinib + Nivo	PD-1	II	Recruiting	05/2020	NCT02940301
Children/Adolescents/Young Adults (≥1 line of therapy, no prior HSCT)	Nivo + BV, followed by BV+Benda in suboptimal responders (CheckMate 744)	PD-1	II	Recruiting	03/2022	NCT02927769
R/R (after SCT or transplant-ineligible)						
R/R cHL (prior auto-HSCT, or transplant-ineligible)	Nivo + BV vs. BV (CheckMate 812)	PD-1	III	NYO	04/2024	NCT03138499
R/R cHL in BV-naive (failed auto-HSCT or transplant ineligible)	Pembro vs. BV (KEYNOTE-204)	PD-1	III	Recruiting	12/2019	NCT02684292
R/R cHL after auto-HSCT and BV, or chemo-refractory with or without prior auto-HSCT)	Pembro	PD	II	Active, not recruiting	04/2021	NCT02453594
Post auto-HSCT	Pembro	PD-1	II	Recruiting	12/2018	NCT02362997
R/R HR cHL	Nivo + BV, to start within 30–60 days of auto-HSCT stem cell infusion	PD-1	II	Recruiting	04/2019	NCT03057795
R/R cHL (transplant ineligible)	Pembro + lenalidomide	PD-1	I	Recruiting	08/2023	NCT02875067

Disease Setting	Regimen	Target	Phase	Status	Est. Study Completion Date	NCT
R/R cHL with prior auto-HSCT or R/R transplant-ineligible	Nivo + lenalidomide	PD-1	Ib	Recruiting	04/2020	NCT03015896
Relapse after allo-HSCT	Ipi or Nivo	CTLA-4, PD-1	I	Recruiting	12/2018	NCT01822509
Relapse after allo-HSCT	Pembro	PD-1	I	Recruiting	02/2020	NCT02981914

Legend: Allo = Allogeneic, AVD = Adriamycin + Vinblastine + Dacarbazine, Benda = Bendamustine, BV = Brentuximab vedotin, Dex = Dexamethasone, Durva = Durvalumab (anti-PDL1), HD = High Dose, HR = High Risk, IFRT = Involved field radiotherapy, ISRT = Involved Site Radiotherapy, IO = immuno-oncology, Ipi = Ipilimumab (anti-CTLA-4), Len = Lenalidomide, MM = Multiple Myeloma, Nivo = Nivolumab (anti-PD-1), NR = Not Reported, NYO = Not Yet Open, Pembro = Pembrolizumab (anti-PD-1), Pom = Pomalidomide, SCT = Stem Cell Transplant, Treme = Tremelimumab (anti-CTLA-4). Status as reported by http://clinicaltrials.gov, accessed 6/12/2017

Table 2

Prospective Clinical Trials of PD-1 blockade in Plasma Cell Myeloma

	Phase	Subgroup	Patients	ORR (≥PR) (%)	CR or sCR n(%)	VGPR n(%)	PR n(%)	SD n(%)	PD n(%)	Median Follow Up (95% CI)	DOR (mo)	Median PFS (95%CI)	Median OS (95% CI)	Ref
Nivolumab CheckMate-039 NCT01592370	Ib	NA	27	0%	0	0	0	17 (63%)	10 (37%)	NR	NA	10	NR	(51)
Pembrolizumab plus Len/Dex KEYNOTE-023 NCT02036502	Ib:	All patients*	50	44%	2(4%)	6 (12%)	14 (28%)	25 (50%)	1 (2%)	18.9 mo (0.8–36)	18.7mo (0.7–30.4)†	7.2 mo (3.9–12.3)	NR (22.4-NR)	(40)
		Len-Refractory population	37	13(35.1%)	2(5.4%)	2 (8.1%)	8 (21.6%)	22 (59.5%)	1 (3.3%)	U	24.9mo (0.7–24.9)††	6.3 mo (2.8–8.5	26.3 mo (22.4-NR)	
		Double or More Refractory	30	13(33.3%)	1(3.3%)	13 (33.3%)	5 (16.7%)	18 (60%)	1 (3.3%)	U	U	U	U	
Pembrolizumab plus Pom/Dex NCT02289222	II	All patients	48 (3 NE)	60%	4(8%)	9 (19%)	16 (33%)	11 (23%)	2(4%)	15.6 (9.2–17.5)	14.7#	17.4mo (11.7–18.8)	NR (18.9-NR) ##	(41)
		Double refractory (PI/IMiD)	32 (73%)	66%	1(4%)	6 (18%)	14 (44%)	U	U	U	U	U	U	
		HR CG	27 (56%)	56%	3(11%)	1 (4%)	11 (41%)	U	U	U	U	15.1mo (9.1–17.9)**	U	

ORR = Overall Response Rate, CR = complete response, sCR = strict complete response, VGPR = very good partial response, PR = partial response, SD = Stable disease, PD = Progressive disease, DOR = duration of response, PFS = progression free survival, OS = overall response, Ref = reference, CG = cytogenetics, NA = not applicable, NE = Not Evaluable, NR = Not reached, U = Unknown.

*2 (4%) of patients were not yet assessable.,

**vs 19 mo (16-NR). for Standard Risk CG,

#= for patients meeting objective response criteria (PR or better),

##as of cut-off date 11/1/2016; 22 (49%) had PD, 9(20%) died, and 23 continue to receive treatment,

†n=22,

††n=13 patients

Table 3

Immune checkpoint blockade and allogeneic stem cell transplantation for relapsed lymphoid malignancies.

	PD-1 blockade Pre Allo		PD-1 blockade Post Allo			CTLA-4 Blockade Post Allo
	Merryman RW et al 2017 (60)	El-Cheikh J et al 2017 (64)	Haverkos et al 2017(62)	Herbaux et al 2017(63)	El Cheikh J et al 2017 (64)	Davids et al 2016(59)
Patients	31 HL, 2 DLBCL, 2FL, 2 PMBCL, 1 EATL, 1 MCL	9 HL	30 HL 1 NHL	20 HL	2 HL	n=28, 7 HL(25%), 4 NHL (14%), 1 MM Myeloid = 20
Med. Time from CBT to allo (range)	62d (7–260)	44d (23–100)	NA	NA	NA	NA
Med. Time allo to CBT (range)	NA	NA	26.4mo (4.8–108)	23 mo(2–111)	10–28 mo	675d (198–1830)
CBT agent n(%)	Nivo 28 (72), Pembro 11 (28)	Nivo 9(100)	28 Nivo 3 Pembro	Nivo (100%)	Nivo 2 (100%)	Ipilimumab 28 (100%)
ORR n(%)	89% HL74%, NHL 13%)	7 (77.8%)	77% (95%CI: 58–90)	95%	2 (100%)	1/12 (lymphoid cancers)
BR to aPD-1 n(%)	CR 14 (36%) PR 10 (26%) SD 7(18%), PD 8 (21%)	CR 4 (44%), PR 3 (33%) SD 0 (0%) PD 2 (22%)	CR: 15(48.4%), PR: 8 (25.8%) SD: 3 (9.7%) PD: 4	CR: 8(42%) PR: 10 (52%)	CR: 2 (100%)	PR: 1/7 in HL
IrAE pre/post allo-HSCT	4(11%), colitis 2(6%), pneumonitis 2 (6%),	NR	17 TE-GVHD (55%)	NR	NR	6 patients (21%) n=1 death Gr5 n=3 pneumonitis (2 Gr2, 1 Gr4) n=1 ITP Gr 2 n=1 diarrhea, Gr 2
Treatment Emergent Gr. 2–4 aGVHD (%, 95%CI)	44%	9(100%)	10 (32%)	6 (30%)	100%	NR, Gut n=1 Gr2
Treatment Emergent Gr. 3–4 aGVHD (%, 95%CI)	23(11–37)	6(66%)	6 (19%)	5 (25%)	2(100%)	0
1 year cGVHD (%, 95%CI)	41(22–60)	NR†	NR	NR	NR	3 cases cGVHD liver (not graded)
1 year TRM (%)	10%*	1 (11%; VOD)	8 (4 aGVHD, 4 cGVHD)	2 (10%)	NR	1 (3.6%)
Median Follow Up (range)	12 (2–33)	10 mo (5–19)	428 (133–833)	370 days (24–486)	1.3–8	15mo (8–27)
1 year OS (%, 95%CI)	89(74–96)	NR	NR (21/31 patients alive at study conclusion; mean 400 days)	78% at 16 mo	NR	49%
PFS (%, 95% CI)	76(56–87) at 1 year	NR	Median PFS 591 days (95%CI: 400–644)	median not reached	NR	17.9%

aGVHD = acute graft versus host disease, CBT = checkboint blockade therapy cGVHD = chronic graft versus host disease, IrAE = immune related adverse event, ITP = immune thrombocytopenia purpura, Nivo = Nivolumab (anti-PD-1), Pembro = Pembrolizumab (anti-PD-1), Ipi = ipilimumab (antiCTLA-4), NA = not applicable, NR = Not Reported, PFS = progression free survival, TRM = treatment related

mortality, VOD = Veno-occlusive disease. *One patient with enteropathy-associated T cell lymphoma received ipilimumab concurrently with anti-PD-1 therapy who died with grade 4 aGVHD, the remained had HL. †two patients had 'mild chronic' GVHD, and one patient had 'severe chronic' GVHD.