



Immune checkpoint inhibitors in lymphoma: challenges and opportunities

Haris Hatic[#], Devi Sampat[#], Gaurav Goyal[^]

Division of Hematology-Oncology, University of Alabama, Birmingham, AL, USA

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[#]These authors contributed equally to this work.

Correspondence to: Gaurav Goyal, MD. Division of Hematology-Oncology, The University of Alabama at Birmingham, 1802 6th Avenue South Suite 2555, Birmingham, AL 35294, USA. Email: ggoyal@uabmc.edu.

Abstract: Immune checkpoint inhibitors (ICIs) are immunomodulatory antibodies that intensify the host immune response, thereby leading to cytotoxicity. The primary targets for checkpoint inhibition have included cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death receptor-1 (PD-1) or programmed cell death ligand-1 (PD-L1). ICIs have resulted in a change in treatment landscape of various neoplasms. Among hematologic malignancies, ICIs have been most successful in certain subtypes of lymphomas such as classic Hodgkin lymphoma (cHL) and primary mediastinal B-cell lymphoma (PMBCL). However, there have been several challenges in harnessing the host immune system through ICI use in other lymphomas. The underlying reasons for the low efficacy of ICI monotherapy in most lymphomas may include defects in antigen presentation, non-inflamed tumor microenvironment (TME), immunosuppressive metabolites, genetic factors, and an overall lack of predictive biomarkers of response. In this review, we outline the existing and ongoing studies utilizing ICI therapy in various lymphomas. We also describe the challenges leading to the lack of efficacy with ICI use and discuss potential strategies to overcome those challenges including: chimeric antigen receptor T-cell therapy (CAR-T therapy), bispecific T-cell therapy (BiTE), lymphocyte activation gene-3 (LAG-3) inhibitors, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) inhibitors, vaccines, promotion of inflammatory macrophages, indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors, DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi). Tumor mutational burden and interferon-gamma release assays are potential biomarkers of ICI treatment response beyond PD-L1 expression. Further collaborations between clinicians and scientists are vital to understand the immunopathology in ICI therapy in order to improve clinical outcomes.

Keywords: Hodgkin; pembrolizumab; nivolumab; ipilimumab; cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)

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[^] ORCID: 0000-0001-6148-5177.

Introduction

The use of immune checkpoint inhibitors (ICIs) has ushered in a paradigm shift in oncology due to successful treatment in various malignancies. After tremendous successes in metastatic melanoma, ICIs were explored in hematologic and other solid organ malignancies. Among solid tumors, ICIs have been approved for treatment of melanoma, renal cell carcinoma, lung cancer, head and neck cancer, gastric cancers, triple-negative breast cancer, urothelial carcinoma, hepatocellular carcinoma, cervical cancer, ovarian cancer, and colorectal cancer (1). However, the efficacy of ICIs in hematologic malignancies has been limited, and mostly seen in certain subtypes of lymphoma (2).

ICIs are immunomodulatory antibodies that intensify the immune system, activate T cell function, and aid in cancer cell death (3). Normally, T-cell activation occurs due to an inciting event such as an infection, inflammation, or malignancy. T-cell activation occurs through the presentation of antigens that are bound on T-cell receptor (TCR) and major histocompatibility complex (MHC) on the surface of antigen-presenting cells (APCs) (4). Next, a complex cascade of pathways is activated, whereby an antigen attaches to a TCR with an ensuing co-stimulation of immune checkpoints in order to provide suppression of the immune response or manage cytotoxicity (5). The balance between the stimulatory and inhibitory signals is mediated via specific membrane receptors or ligands on T-cell surface (6). These specific ligands include cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death-1 (PD-1) (7).

Mechanism of action

To discern the mechanism of action of ICIs, it is crucial to understand how the CTLA-4 and PD-1 ligands play a role in the immune response. CTLA-4 regulates T-cell proliferation early in an immune response, primarily in lymph nodes, whereas PD-1 suppresses T-cells later in an immune response, primarily in peripheral tissues (4). CTLA-4 works by indirectly diminishing signaling through its co-stimulatory receptor, CD28 (*Figure 1*). As such, CTLA-4 increases the activation threshold of T cells, reducing immune responses to weaken antigens such as self- and tumor antigens (7). PD-1 attaches to programmed death-ligand 1 (PD-L1), a protein on some normal (and cancer) cells. The PD-1/PD-L1 interaction then inhibits T-lymphocyte proliferation, survival and effector functions

such as cellular toxicity and cytokine release (7).

Various ICIs are available that target specific immune checkpoints: anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab), and anti-PDL-1 (atezolizumab, avelumab, and durvalumab). Ipilimumab was the first ICI to be approved in oncology due to robust responses demonstrated in metastatic melanoma (8). While most responses with ICIs were reported in solid organ malignancies, lymphomas have the most outcomes data among the hematologic neoplasms. In May 2016, nivolumab was approved for treatment of classic Hodgkin lymphoma (cHL) in patients with relapse after autologous hematopoietic stem cell transplant (AHSCT) (9). The following year in March 2017, pembrolizumab was approved for the treatment of relapsed/refractory classic HL (r/r cHL) after 3 or more prior lines of therapy, and most recently in 2020 this was extended to failure of one line of therapy (9). The only other approved indication of ICIs in lymphoma is pembrolizumab in primary mediastinal B-cell lymphoma (PMBCL) after failure of 2 or more lines of therapy. Over the last few years, our understanding of the immune biology and role of ICIs in lymphoma has grown.

In this review, we provide a comprehensive overview of the extant literature using ICI therapy in lymphoma, with focus on key endpoints like overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). We also discuss the challenges associated with ICI therapy in lymphomas, and the strategies to overcome those challenges in order to improve their efficacy.

Efficacy of ICIs in lymphoma

cHL

Around 80% of patients with cHL can be cured by first line therapy alone; however, challenges in cHL arise when selecting what agents should be used for refractory or relapsed disease. Among lymphomas, ICIs have demonstrated robust responses particularly in cHL (10). The reasons for the remarkable responses seen with ICI therapy in cHL are potentially multifold. The Reed Sternberg cells (RSC) of cHL attract a rich immune infiltrate of CD4/CD8 cells surrounding them. RSC are characterized by two major immune pathways: nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and Janus kinase (JAK) pathways which further amplify PD-L1 expression (10). It is also important to note that the chromosomal region 9p24.1 that contains both the

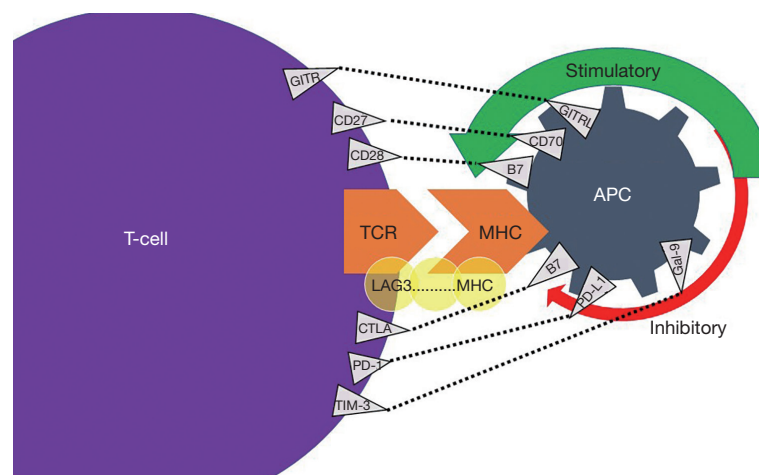


Figure 1 Inhibitory & stimulatory T-cell cognate ligand receptors. Some known stimulatory and inhibitory ligands on TCR. Some of the upregulators of T-cells and their cognate ligand are CD27-CD70, GITR-GITRL, CD28-B7, ICOS-ICOSL. Inhibitory TCRs and their ligand include: LAG3-MHC, CTLA4-B7, PD1-PDL1, TIM3-Gal9. CTLA 4, cytotoxic T-lymphocyte associated protein 4; GITR, glucocorticoid-induced tumor necrosis factor receptor; GITRL, glucocorticoid-induced tumor necrosis factor receptor ligand; MHC, major histocompatibility complex; LAG3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; PDL-1, programmed death ligand 1; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; TCR, T-cell receptor; Gal9, galectin-9.

PD-L1 and PD-L2 genes is amplified in RSCs, resulting in overexpression of both proteins. Another theory for high efficacy of ICIs in cHL is based on its association with Epstein-Barr virus (EBV). EBV infection in cHL might potentially increase the PD-L1 expression such that blocking the PD-1 and PDL-1 pathway may restore immunosurveillance in cHL (10).

At least four different phase I-II trials have showed ORR of >70% using anti PD-1 therapy (10-13). The first landmark study by Ansell *et al.* enrolled 23 patients with heavily pre-treated relapsed or refractory cHL to receive nivolumab, and demonstrated an ORR of 87%, including 17% with a complete response (CR) and 70% with a partial response (PR) (10). The rate of progression-free survival at 24 weeks was 86% (10). Subsequent studies using nivolumab, pembrolizumab or a combinational therapy with PD-1 and CTLA-4 blocking agents showed sustained remissions in responders (*Table 1*) (14-16). A recent study showed superior PFS with the use of pembrolizumab as compared with brentuximab vedotin for r/r cHL after one line of therapy among patients ineligible for AHSCT (38). These studies have resulted in regulatory approval of nivolumab after 2 lines of treatment including autologous stem cell transplant and brentuximab vedotin, and of pembrolizumab after one line of therapy. In a phase I/II trial evaluating the efficacy of nivolumab and brentuximab

vedotin on refractory/relapsed cHL, 61% of patients achieved a CR, with an ORR of 82% (N=62) (12). Due to the high response rates, ongoing studies are evaluating the role of ICIs in combination with chemotherapy in the frontline or salvage therapy of cHL (*Table 2*).

Diffuse large B-cell lymphoma (DLBCL)

Anti-PD-1 antibodies pembrolizumab and nivolumab have been evaluated in DLBCL as well, though with suboptimal responses. PD-L1 overexpression is observed in about of 20% of DLBCL and occurs primarily on macrophages (39). Kiyasu *et al.* examined over 1,250 DLBCL samples using PD-L1 and PAX5 staining techniques and found that 10.5% of patient specimens expressed PD-L1 and this increased to about 15% when the microenvironment was included with a threshold for PD-L1 positivity set at 30% (40). The variability of PD-L1 expression in DLBCL is dependent on the subtype and threshold of PD-L1 positivity. Structural changes of 9p24.1 leading to PD-L1 expression are seen in 10% of patients, and mostly in the non-germinal center type of DLBCL (41). However, there have been several studies involving ICI treatments in DLBCL with varied results (*Table 1*) (13,17-21). Although the initial phase I study showed an ORR of 36% with nivolumab (21), subsequent phase II studies revealed a dismal ORR <10%

Table 1 Cumulative data of immune checkpoint inhibitors in lymphoma

Disease	Phase	Drug Used	Checkpoint Target	No of pts	ORR	CR	PFS mo	OS mo	DOR mo	Comments	Reference
cHL	Phase 1	Nivolumab	Anti-PD-1	23	87%	17%	86% at 6 mos	NR	DOR not yet reached. 47% of patients with ongoing responses	Relapsed or refractory, 78% patients relapsed post HSCT. 78% patients relapsed post Brentuximab.	Ansell et al., 2015 (10)
cHL	Phase 1	Nivolumab	Anti-PD-1	95	65%	7%	14.7	NR	8.7	Relapsed or refractory, serious adverse events were high, reported in 21% of patients in this study.	Kasamon et al., 2017 (14)
cHL	Phase 1	Nivolumab + BV	Anti-PD-1	18	89%	50%	N/A	5.5	NR	Relapsed or refractory	Diefenbach et al., 2016 (11)
cHL	Phase 1/2	Nivolumab + BV	Anti-PD-1	62	82%	61%	89% at 6 mos	5.3	NR	Relapsed or refractory, peripheral blood biomarker analysis was done in this study.	Herrera et al., 2018 (12)
cHL	Phase 1 /Keynote 13	Pembrolizumab	Anti-PD-1	31	65%	17%	45% at 13 mos	100% at 6 mos	70% DOR >6 mos	Relapsed or refractory, Pembro dosage was every 2 weeks at 10 mg/kg until progression	Armand et al., 2016 (15)
cHL	Phase 2 /Keynote 87	Pembrolizumab	Anti-PD-1	210	69%	22%	8.6	6	NR	Relapsed or refractory, large study with primary end point of ORR. PDL-1 positivity was not required for enrollment.	Chen et al., 2017 (16)
cHL	Phase 1	Nivolumab + ipilimumab	Anti-PD-1 & anti-CTLA-4	31	74%	19%	7.2	NR	NR	Relapsed or refractory, predominantly transplant naïve group	Ansell et al., 2016 (13)
DLBCL	Phase 2	Pidilizumab	PD-1	66	51%	68%	72% at 16 mos	16	N/A	treatment after auto-HSCT	Armand et al., 2013 (17)
DLBCL + FL	Phase 1b	5F9 + rituximab	CD47	22	50%	36%	7	NR	NR	Maximum tolerated dose not reached	Advani et al., 2018 (18)
DLBCL	Phase 2	Nivolumab	PD-1	34	3%	N/A	1.4	5.8	8	Relapsed/refractory; transplant ineligible	Ansell et al., 2019 (19)
FL	Phase 1b/2	Durvalumab + ibrutinib	Anti-PD-1	27	26%	10.2	10.2	NE	11	Transplant failed	Herrera et al., 2020 (20)
GCB-DLBCL				16	13%	2.9	2.9	5.5	NE	Majority of pts had DLBCL	

Table 1 (continued)

Table 1 (continued)

Disease	Phase	Drug Used	Checkpoint Target	No of pts	ORR	CR	PFS mo	OS mo	DOR mo	Comments	Reference
Non-GCB DLBCL				16	38%		4.1	7.3	NE	Highest ORR in non-GCB subset	
DLBCL	Phase 1	Nivolumab	Anti-PD-1	11	36%	18%	0.3	NE	NE	Relapsed or refractory	Lesokhin et al., 2016 (21)
DLBCL	Phase 1	Nivolumab + ipilimumab	Anti-PD-1 & anti-CTLA-4	10	20%	0%	2.9	1.5	NR	Relapsed or refractory	Ansell et al., 2016 (13)
PMBCL	Phase 1	Pembrolizumab	Anti-PD-1	21	48%	33%	10.4	31.4	NR	Relapsed or refractory, failed or ineligible for transplant	Armand et al., 2020 (22,23)
PMBCL	Phase 1/2	Nivolumab + BV	Anti-PD-1	30	70%	37%	63.5% at 6 mos	86.3% at 6 mos	NR	Relapsed or refractory	Zinzani et al., 2019 (24)
CLL	Phase 1	Pembrolizumab	Anti-PD-1	16	0%	0	2.4 m	11.2 m	NR	Closed early	Ding et al. 2017 (25)
CLL	Phase 2	Nivolumab & ibrutinib	Anti-PD-1	5	60%	0	NR	NR	N/A	Very small study involving CLL only patients	Jain et al., 2016 (26)
FL	Phase 2	Pidilizumab + rituximab	PD-1	32	66%	52%	18.8	Not met	20.2	Allowed further optional infusions of Pidilizumab for stable disease patients	Westin et al., 2014 (27)
FL	Phase 1	Nivolumab	Anti-PD-1	10	40%	10%	NR	NR	6-81 weeks	n/a	Lesokhin et al., 2016 (21)
FL	Phase 1	Nivolumab + ipilimumab	Anti-PD-1 & anti-CTLA-4	5	20%	0	1.5 m	2.9 m	NR	Small group of patients	Ansell et al., 2016 (13)
FL	Phase 2	Pembrolizumab + rituximab	Anti-PD-1	30	80%	60%	NR	NR	NR	n/a	Nastoupil et al., 2017 (28)
FL	Phase 2	Atezolizumab + obinatumab	Anti-PD-1	26	57%	N/A	N/A	N/A	N/A	PD-L1 and MHC1 expression did not correlate with response in this study.	Palomba et al., 2017 (29)
T-cell lymphoma	Phase 2	Pembrolizumab	Anti-PD-1	9	55%	0	12	NR	NR	MF	Khodadoust et al., 2020 (30)
EBV Lymphoma	Phase 1	Pembrolizumab	PDL-1	30	24%	17%	NR	NR	NR	EBV	Kim et al., 2019 (31)
EBV NK/ T-cell Lymphoma	Phase 1	Pembrolizumab	PDL-1	7	100%	29%	NR	NR	NR	EBV	Kwong et al., 2017 (32)

Table 1 (continued)

Table 1 (continued)

Disease	Phase	Drug Used	Checkpoint Target	No of pts	ORR	CR	PFS mo	OS mo	DOR mo	Comments	Reference
NHL	Phase 1	Pembrolizumab	Anti-PD-1	5	40%	0	NR	NR	NR	HIV	Uldrick et al., 2019 (33)
r/r HL or NHL	Case series	Nivolumab	Anti-PD-1	7	83%	60%	NR	10.3 m	NR	HIV	Rogacheva et al., 2019 (34)
T-cell lymphoma	Phase 1b	Nivolumab	Anti-PD-1	23	17%	0	2.5 m	NR	NR	relapsed or refractory cutaneous T-cell lymphoma (n=5), mycosis fungoides (n=13), and peripheral T-cell lymphoma (n=5)	Lesokhin et al., 2016 (21)
NK/T-cell lymphoma	Phase 1	Pembrolizumab	Anti-PD-1	7	100%	71%	NR	NR	NR	Average size study for NK/T cell	Kwong et al., 2017 (32)
T-cell lymphoma	Phase 2	Pembrolizumab	Anti-PD-1	15	27%	7%	12	NR	NR	SS	Khodadoust et al., 2020 (30)
r/r HL or NHL	retrospective	Pembrolizumab or nivolumab	Anti-PD-1	39	62%	36%	10.7 m	9.1 m	NR	Allogenic HSCT w/post ICI treatment	Merryman et al., 2017 (35)
r/r HL	retrospective	Pembrolizumab or nivolumab	Anti-PD-1	21	43%	NR	NR	NR	NR	Allogenic HSCT w/post ICI treatment	Holderried et al., 2019 (36)
Lymphoma post SCT	Phase 2	Revlimid + Iplimumab	CTLA-4	10	70%	40%	56% at 12 mos	NR	NR	Allo-HSCT	Khouri et al., 2018 (37)
				7	100%	14%	86% at 12 mos	NR	NR	Auto-HSCT	

ORR, overall response rate; CR, complete response; PFS mo, progression free survival in months; OS mo, overall survival in months; DOR mo, duration of response in months; cHL, classical Hodgkin lymphoma; DLBCL, diffuse large b-cell lymphoma; FL, follicular lymphoma; GCB, germinal center b-cell; PMBCL, primary mediastinal b-cell lymphoma; CLL, chronic lymphocytic leukemia; NK cell, natural killer; EBV, Epstein Barr virus; NHL, non Hodgkin lymphoma; r/r, relapsed refractory, SCT, stem cell transplant; BV, brentuximab vedotin; 5F9, Hu5F9-G4 macrophage immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PDL-1, programmed death ligand 1; CTLA 4, cytotoxic T-lymphocyte associated protein 4.

Table 2 Current trials involving immune checkpoint inhibitors

Disease	Phase	Drug used	Checkpoint target	Comments	Clinical trial	Status
Hodgkin lymphoma	Phase II	Nivolumab	Anti-PD-1	Combination of nivolumab and DHAP in patients with relapsed or refractory classical Hodgkin lymphoma	NCT04091490	Not yet recruiting
Hodgkin lymphoma	Phase II	Pembrolizumab	Anti-PD-1	A phase II study to determine pembrolizumab as frontline treatment of patients with Hodgkin lymphoma	NCT03331731	Not yet recruiting
Hodgkin lymphoma and diffuse large B cell lymphoma	Phase I	Pembrolizumab	Anti-PD-1	A study of pembrolizumab in participants with relapsed or refractory primary mediastinal large B-cell lymphoma	NCT04317066	Recruiting
Lymphoma, non-Hodgkin; multiple myeloma	Phase II	Olaparib, dasatinib, nivolumab plus ipilimumab	Anti-PD-1 & anti-CTLA-4	Canadian profiling and targeted agent utilization trial	NCT03297606	Recruiting
Hodgkin lymphoma and diffuse large B cell lymphoma	Phase I	TAA-T cells and Nivolumab	Anti-PD-1	Tumor associated antigen specific T cells with pd1 inhibitor for lymphoma	NCT03843294	Recruiting
B cell lymphomas	Phase I	Nivolumab	Anti-PD-1	Microtransplantation and checkpoint blockade immunotherapy for relapsed or refractory B cell lymphomas	NCT03920631	Recruiting
Relapsed/refractory diffuse large B cell lymphoma	Phase I/II	Nivolumab plus ipilimumab	Anti-PD-1 & anti-CTLA-4	Nivolumab/ipilimumab-primed immunotransplant for DLBCL	NCT03305445	Recruiting
Diffuse large B-cell lymphoma	Phase I	Pembrolizumab + tisagenlecleucel	Anti-PD-1	Study of tisagenlecleucel in combination with pembrolizumab in r/r diffuse large B-cell lymphoma patients	NCT03630159	Recruiting
Primary central nervous	Phase II	Pembrolizumab	Anti-PD-1	Study on pembrolizumab for recurrent primary central nervous system lymphoma	NCT02779101	Unknown
Follicular lymphoma	Phase I	Nivolumab	Anti-PD-1	Nivolumab plus rituximab in first-line follicular lymphoma	NCT03245021	Recruiting
Mantle cell	Phase I/II	Nivolumab + lenalidomide	Anti-PD-1	Nivolumab and lenalidomide in treating patients with relapsed or refractory NH or HL	NCT03015896	Recruiting
Mantle cell	Phase I/II	Ibrutinib + pembrolizumab	Anti PD-1	Ibrutinib and pembrolizumab in treating patients with relapsed or refractory mantle cell lymphoma	NCT03153202	Recruiting
T/NK-cell lymphomas NK-cell lymphomas	Phase II	Pembrolizumab	Anti-PD-1	Pembrolizumab for T/NK-cell lymphomas NK-cell lymphomas	NCT03021057	Recruiting
Peripheral T cell lymphoma	Phase I/II	Nivolumab and EPOCH	Anti PD-1	Nivolumab with standard of care chemotherapy for peripheral T cell lymphomas	NCT03586999	Recruiting

Table 2 (continued)

Table 2 (continued)

Disease	Phase	Drug used	Checkpoint target	Comments	Clinical trial	Status
Aggressive B cell lymphoma	Phase II	Varilumab +/- nivolumab	Anti PD-1	Nivolumab with or without varilumab in treating patients with relapsed or refractory aggressive B-cell lymphomas	NCT03038672	Recruiting
Multiple myeloma and lymphoma	Phase I/II	Nivolumab plus ipilimumab	Anti-PD-1 & anti-CTLA-4	Check point inhibition after autologous stem cell transplantation in patients at high risk of post transplant recurrence	NCT02681302	Recruiting

TAA-T cells, tumor associated antigen specific T cells; PD-1, programmed cell death protein 1; PDL-1, programmed death ligand 1; CTLA 4, cytotoxic T-lymphocyte associated protein 4; NK cell, natural killer; DHAP, dexamethasone, high dose cytarabine, platinum.

with ICI monotherapy (Table 1). Although there are several ongoing studies examining the combination of ICIs with other agents in DLBCL, there is a need to identify predictive biomarkers to identify patients that will benefit from such an approach.

PMBCL

ICI therapy has also been evaluated in PMBCL, which is the only other lymphoma subtype than cHL to show robust responses with ICI therapy. This is perhaps in part because PMBCL frequently expresses PD-L1/2, which is not seen in most other mature B-cell lymphomas. Approximately 30–80% of patients with PMBCL have PD-L1 overexpression (42). PMBCLs also share pathologic and genetic features with cHL. In a phase I study (Keynote 013), the ORR with anti PD-1 therapy in relapsed/refractory PMBCL was 48%, with median OS of 31.4 months (22) (Table 1). This study led to the approval of pembrolizumab by the US-FDA in PMBCL patients after failure of 2 or more lines of therapy. Another trial utilized a combination of nivolumab and brentuximab vedotin, with ORR of 70%, CR of 37%, and median OS not reached at 11 months follow-up (24). However, both these trials had a small sample size, and there is a need for larger studies as well as long-term follow-up data supporting ICI use in this disease.

Primary central nervous system lymphoma (PCNSL) and testicular lymphoma (PTL)

PCNSL and PTL demonstrate high expression of PD-L1 and PD-L2 through amplification 9p24.1, which makes it attractive to use ICI therapy (43). Nivolumab was tested in four patients with PCNSL and one patient with PTL in the relapsed/refractory setting. Interestingly, all five patients had an objective response, with three patients in ongoing remission over one year. There is a current phase II study underway with pembrolizumab in relapsed/refractory PCNSL (Table 2, NCT02779101).

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and richter transformation

In CLL/SLL, anti-PD1 therapy using pembrolizumab has been examined in various trials. PD-L1/PD-1 expression in CLL/SLL can range between 10–90% (44,45). Effector memory T-cells in CLL are impaired, thus cannot form immune synapse with CLL cells which is reflected in

PD-L1 overexpression in the tumor microenvironment (TME) of histiocytes (46). This large variability of PD-L1 expression is likely secondary to differences in antibodies used, methodology employed, and staining specificity (47). Nevertheless, in aggressive cases of CLL/SLL, there is an expansion of CD8+/PD-1 and T memory cells that subsequently inverts the CD4:CD8 ratio (48). It seems that increased PD-L1 expression on T-cells had no prognostic significance (49). In a phase II study, pembrolizumab was administered to relapsed CLL and Richter transformation (RT) patients (25). The study demonstrated an ORR of 44% and a median OS of about 11 months among RT cohort (*Table 1*). However, no responses were seen among CLL cohort in this study. In this study, higher PD-L1 expression on tumor cells and microenvironment was associated with a response to ICIs in RT (25). There is some evidence to suggest that using BTK inhibitors before ICIs may increase the efficacy of ICIs, though further studies are needed to confirm this finding (26,50).

Follicular lymphoma (FL)

The expression of PD-1 and PDL-1 on tumor cells of FL is rare. Several studies have examined the role of ICIs in relapsed/refractory FL (*Table 1*) (13,21,27-29). In an open-label non-randomized trial of 32 patients with relapsed FL, pidilizumab was administered with rituximab weekly for 4 weeks (27). The ORR was 66% and CR was 52% with median PFS of 18.8 months (27). In another phase Ib trial, 5 patients with relapsed/refractory non-Hodgkin lymphoma (NHL) received nivolumab plus ipilimumab followed by nivolumab monotherapy (13). In this study, the ORR was 20%, with a PFS of 1.5 months and OS of 2.9 months. However, when studied in phase II trial of 92 patients, the ORR was 4%, with median PFS of 2.2 months with nivolumab monotherapy (51).

Mantle cell lymphoma (MCL)

While preclinical studies have suggested a mechanistic role for ICIs in patients with MCL, clinical data thus far suggests only modest success. The expression of therapeutically targetable immune checkpoint molecules has been analyzed on primary MCL cells. MCL cells showed constitutive expression of PD-1 and PDL-1, but absence of PD-L2 and CTLA-4 (52). Furthermore, it was found that induction of PD-L1 was attenuated by concurrent treatment with

ibrutinib or duvelisib, suggesting BTK and PI3K are important mediators of PD-L1 expression (52). To date, there are no completed trials of immunotherapy treatments specifically for MCL patients, however, several trials have included a small subset of MCL patients to assess efficacy of ICIs. In a phase I trial of nivolumab in relapsed/refractory NHLs, no responses were seen among the four patients with MCL (21). An ongoing trial is using lenalidomide and nivolumab to assess safety and response in patients MCL (*Table 2*). Another clinical trial is looking at BTK inhibitor combined with pembrolizumab for relapsed or refractory MCL (*Table 2*).

Burkitt lymphoma (BL)

BL is well known to be a highly aggressive lymphoma in which rapid, high intensity chemotherapy is standard of care. Typically, aggressive chemotherapy regimens used for this disease can put young, functional patients in complete remission with low proportion of primary refractory disease. ICIs have not been utilized outside the context of clinical trials for these patients. The ongoing trial that has been partly reported involves varlilumab or CDX-1127, a fully human monoclonal antibody that binds to a molecule called CD27 found on T-cells and also on certain hematologic tumor cells to promote anti-tumor effects. The trial initially assessed safety in phase I, and it has now moved onto phase II utilizing nivolumab with or without varlilumab in aggressive b-cell lymphomas, including BL (*Table 2*).

Epstein Barr virus (EBV)-associated lymphoma

EBV, or human herpesvirus, has infected over 90% of adults worldwide and remains lifelong in the latent phase (53). In a small percentage of patients, it can lead to BL, cHL, lymphoproliferative disease (LPD) in immunodeficient individuals, and DLBCL (54). Latent EBV infections can transmit through infected tumor cells and cause inflammation in the TME. In cHL associated with EBV, dendritic cells (DCs) and tumor associated macrophages (TAM) are detected in tumor specimens (55). In extranodal NK/T-cell lymphoma, nasal type (ENKL), the EBV activates latent membrane protein-1 (LMP1) which induces NF- κ B to produce T-helper cell-1 (TH1) cytokines tumor necrosis factor-alpha (TNF- α) and interferon gamma (IFN- γ) (56). In ENKL there is an upregulation of PD1 in order to suppress T cell toxicity (56). EBV infection has

been reported to upregulate PDL-1 expression and PD-L1/PD-L2 gene alterations in a large proportion of lymphomas (57-59). For instance, in DLBCL, PD-L1 was expressed in about 60% of cases and on average 20% of patients had a PD-L1/PD-L2 genetic expression in EBV-positive lymphoma (58,60).

In a study of relapsed or refractory NK/T cell lymphoma using pembrolizumab (*Table 1*), CR rate was 71.4% and two patients had molecular remission (32). In another trial, seven patients with EBV+ NHL showed a response including NK/T cell lymphoma (44%) and primary mediastinal B cell lymphoma (25%). EBV-negative subtypes of DLBCL and T-lymphoblastic lymphoma did not respond (31). Also, PD-L1 expression was 56% in EBV+ compared to EBV- patients whose expression level was 11% (31).

Human immunodeficiency virus (HIV)-associated-lymphoma

Antiretroviral therapy (ART) has dramatically improved HIV management and outcomes. Interestingly, CTLA-4 and PD-1 expression tends to correlate with HIV viral load, number of CD4+ cells, and disease progression (61). In a small study, it was found that HIV RNA increased with ICI therapy due to latency reversal (4). PD-L1 expression is the highest in HIV patients with or without an EBV co-infection in B-cell lymphoma (62). Most trials of ICIs exclude people living with HIV, which make the use of ICIs a challenge as questions related to side-effects, medication interactions and outcomes remain unanswered.

A recent phase I trial (*Table 1*) examined the safety profile of pembrolizumab for HIV malignancies (33). Of the five patients with NHL in the trial, PRs were seen in four patients (including one patient with primary effusion lymphoma) (33). No unique toxicities were reported in this cohort. These results showed that ICIs can be used safely among people living with HIV and cancer. In a case series, nivolumab use was reported as salvage therapy in relapsed/refractory cHL (n=4) and NHL (n=2) (34). In the case series, two patients received monotherapy (both cHL) with nivolumab, while the rest received the combination of nivolumab with bendamustine and gemcitabine. The ORR was 83%, and 60% achieved a CR (*Table 1*). Among the two patients with cHL who received nivolumab monotherapy, one achieved a CR and other a PR. These limited data are a first crucial step in the investigation of ICIs among people living with HIV and lymphoma.

T-cell lymphoma

Although ICI therapy relies on activation of exhausted T-cells, there are data to suggest that tumor cells of T-cell lymphomas express PD-1, with frequent copy number losses of PD-1 in cutaneous T-cell lymphomas (63). In an early phase basket study, the ORR rates using nivolumab were 15% and 40% among patients with mycosis fungoides and peripheral T-cell lymphomas (PTCL), respectively (21).

A subsequent study evaluating outcomes among PTCL using nivolumab was presented at American Society of Hematology meeting in 2019. Unfortunately, hyperprogression (defined as dramatic progression within 1 cycle of treatment) was noted in one-third patients (n=4), which led to halting of the study (64). In a phase II trial of pembrolizumab among patients with advanced Sezary syndrome, ORR was 38% with two CRs and seven PRs. Of the responding patients, six had 90% or more improvement in skin disease (30). Therefore, ICI therapy deserves further exploration in cutaneous T-cell lymphomas (*Table 1*) (21,30,32).

Autologous/allogenic hematopoietic stem cell transplantation

Given the immune remodeling and low tumor burden after AHSCT, various studies have examined the role of ICIs post-AHSCT in lymphoma. In a phase II study, pidilizumab (anti PD-1 antibody) was utilized post-AHSCT in DLBCL patients (17). Among the 35 patients with measurable disease post-AHSCT, the ORR was 51%. Among the entire cohort, the PFS at 16 months was 72%, suggesting a potential role of ICI therapy in this setting especially in high-risk patients (17). Another vital question with use of ICIs arises in the allogeneic hematopoietic stem cell transplant (HSCT) setting, due to concerns for potential worsening of graft-versus-host-disease (GVHD). In a multicenter retrospective analysis of 39 lymphoma patients (79% cHL) who received ICI treatment prior to allogeneic HSCT, the ORR with PD-1 blockade was 78%, with 41%CRs (35). The two-year OS and PFS were 79% and 65%, respectively (35). The one-year cumulative incidence of grade 3-4 acute GVHD was 23%, and that of chronic GVHD was 41% (35). There are several studies that indicate an increase in GVHD due to enhancement from the IFN- γ dependent mechanism (65-67). In a multicenter retrospective study of 31 lymphoma patients (94% cHL) who received ICI therapy post-allogeneic HSCT,

55% patients developed treatment-emergent GVHD that was refractory to most treatments in majority of cases (66). Further studies are required to confirm these findings with a longer follow-up periods that examine outcomes, complications and risk factors for toxicity (*Table 1*) (35-37).

Challenges limiting the efficacy of ICI therapy in lymphoma

Antigen presentation

Defective antigen presentation is likely the leading factor and explanation for reduced efficacy of ICI therapy specifically in lymphomas. This is because it is common to have a loss of MHC-I on the lymphoma cell surfaces, ultimately due to irreversible mechanisms such as alterations in the MHC-I gene itself and mutations in the B2-microglobulin ($\beta 2M$). On a broad level, lymphomas can evade the immune system recognition through the downregulation of molecules involved in antigen presentation (68). Loss of MHC-I on the surface of CD8+ cells occurs in about 60% of DLBCL and cHL (69). The main reason for this is a loss-of-function mutation of the $\beta 2M$ which occurs in about 20% of FL, 30% of BL, 30% of DLBCL, 50% of PMBCL, and at least 50% of HL (70-72). Likewise, downregulation of MHC-II occurs via mutations in the class II transactivator (CIITA) (73). Defective antigen presentation can also be caused by gamma-interferon-inducible-lysosomal thiol reductase (GILT) and human leukocyte antigen DM (HLA-DM) (74). These two enzymes of the antigen processing machinery are downregulated by c-MYC (74). Apart from further research to overcome this immune evasion, a potential alternative would be monotherapy or combination therapy with MHC-independent treatments such as chimeric antigen receptor T-cell therapy (CAR T-cell therapy) or bispecific T-cell engager antibodies (BiTEs) (*Figure 2*). CAR-T therapy uses a patient's own T-cells to attack the tumor cells via a CAR molecule, and have been approved for relapsed/refractory DLBCL and MCL. BiTEs represent a bridge by targeting an antigen on lymphoma and another on T-cells in order to induce cell-mediated cytotoxicity. In a phase I trial of relapsed/refractory B-cell NHL patients using BiTE antibody, there was an ORR of 69% and CR 37% with median duration of response (DOR) of 17 months (75).

Combinational treatment using ICIs can be approached in two specific ways. First, ICIs can be combined with chemotherapy, monoclonal antibody, targeted therapy, or

CAR-T cell therapy in order to induce antigen presentation by APC (76). Some of the combination trials with ICIs include ibrutinib (NCT02950220, NCT02940301), PI3K inhibitors (NCT03471351), lenalidomide (NCT02875067), and anti-CD20 antibody (NCT03121677) (20,21). The second way that combinational treatment can be utilized is through the use of two ICIs which can potentially overcome the issue of defective antigen presentation by enhanced T-cell activation. However, special care should be taken to avoid lymphocyte depleting regimens as they can be counter-productive in this setting.

TME and tumor associated macrophages

The TME may also determine the immune response to ICI therapy. Most lymphomas, such as DLBCL, FL, CLL, and BL harbor a "noninflamed" microenvironment which is defined by a low infiltration of immune cells with a plethora of genetic escape alterations (68). These excluded immune cells can further promote tumor proliferation through cytokines, chemokines, myeloid-derived suppressor cells (MDSCs), and tumor-infiltrating lymphocytes (TILs) (77).

T-cell response is also dependent on co-receptors (*Figure 1*). Some of the upregulators of T-cells and their cognate ligand are CD27-CD70, GITR-GITRL, CD28-B7, ICOS-ICOSL, CD137-CD137L, and OX40-OX40L (78). Inhibitory TCRs and their receptive cognate ligand include: LAG3-MHC, CTLA4-B7, PD1-PDL1, TIM3-Gal9, and BTLA-HVEM (78). PD-1 blockade resistance can occur via lymphocyte activation gene-3 (LAG-3) and T cell immunoglobulin and mucin-domain containing-3 (TIM-3) (79). LAG-3 is a competitor of CD4 and binds to MHC-II. In EBV+ cHL, LAG-3 is expressed on the T cells and associated with reduced CD8+ response which is currently being examined in a series of phase I/II trials (79-81) (NCT03311412). Also, in lymphoma TIM-3 upregulation on CD8+ T-cells and TILs leads to tumor resistance, which is a process that could be reversed with combinational blockade of PD-1 and anti-TIM-3 monoclonal antibodies (82) (NCT03489343).

In relapsed cHL, there are increased number of PD-1 positive T cells and continuous TCR stimulation from high antigen exposure can lead to exhaustion of effector T-cells (83). Modulating the TME can be a solution to how this resistance could be overcome. A CTLA-4 inhibitor could be used to induce regulatory T cell (Treg) depletion (84). Treg infiltration can be reduced by a low dose of cyclophosphamide through downregulation of

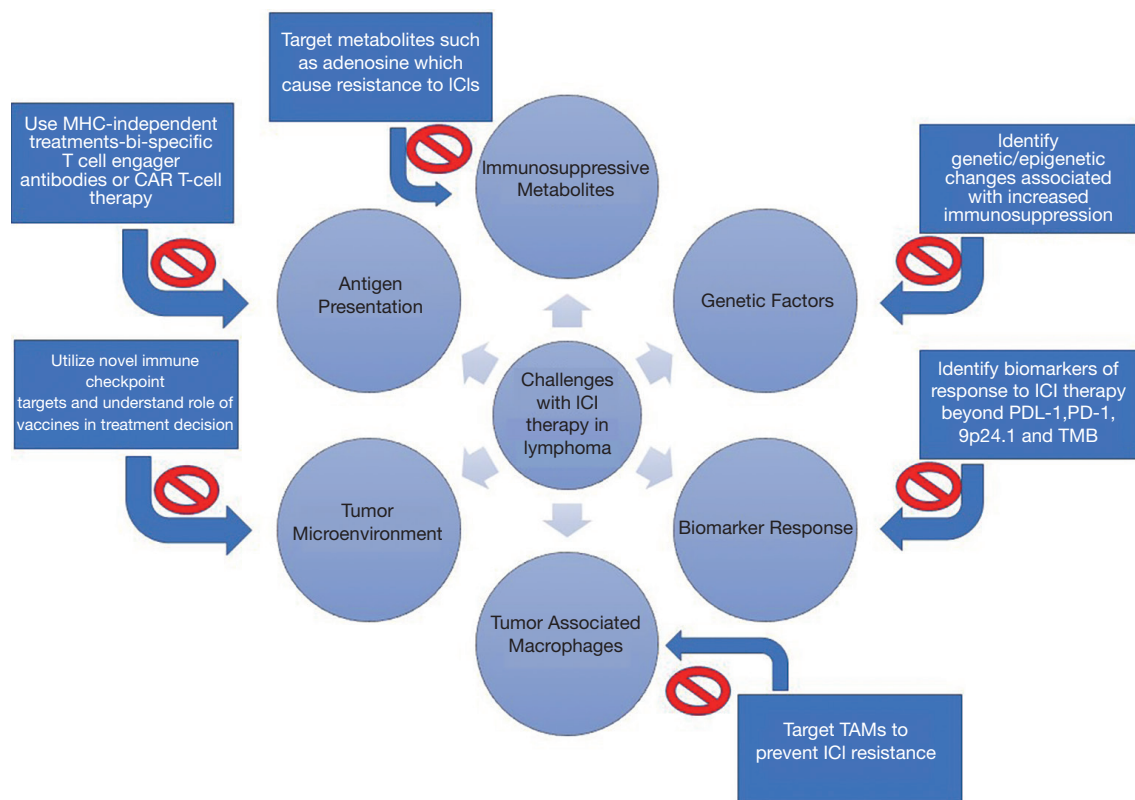


Figure 2 Challenges with immune checkpoint inhibitors therapy and strategies to overcome those challenges. There are six specific challenges with immune checkpoint inhibitors (ICIs) and they include: antigen presentation, tumor microenvironment (TME), tumor associated macrophages (TAM), immunosuppressive metabolites, genetic factors and biomarker response. For each of the challenges specific strategies are described that can overcome it. For antigen presentation the use of major histocompatibility complex independent treatment can be used such as chimeric antigen receptor T-cell therapy (CAR T-cell therapy) or Bispecific T-cell engager antibodies (BiTE). For TME challenges, novel checkpoint inhibitors can be used such as lymphocyte activation gene-3 (LAG-3) and T cell immunoglobulin and mucin-domain containing-3 (TIM-3) inhibitors with programmed death ligands. Vaccines are also investigated to overcome this challenge. Use of anti-CSF antibodies or the promotion of inflammatory macrophages through phosphatidyl 3-kinase- γ inhibitors can counteract TAMs resistance. Immunosuppressive metabolite such as indoleamine 2,3-dioxygenase 1 (IDO1) can be bypassed by an inhibitor such as epacadostat. Microarrays can identify specific genes much easier and allow of analysis of the TME for assessment of immune evasion. Epigenetic therapies can overcome some of those changes through DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi). Lastly, newer biomarkers are being identified such as serum IFN- γ levels and number of CD8-positive monocyte tumor infiltrating lymphocytes (TILs) on the tumor sample. ICI, immune checkpoint inhibitor; CAR-T, chimeric antigen receptor T cell; MHC, major histocompatibility complex; SNP, single nucleotide polymorphisms; PD-1, programmed cell death protein 1; PDL-1, programmed death ligand 1; TMB, tumor mutational burden; TAM, tumor associated macrophages; IO, immunotherapy.

forkhead box P3 (FOXP3) (85).

TAMs promote immunosuppression and phagocytosis. They are divided into M1 (pro-inflammatory) and M2 (anti-inflammatory) subsets. M2 macrophages are CD163+ and are recruited by upregulation of interleukin 10 (IL-10) (86). In cHL, the presence of CD163+/CD68+ macrophages in the TME was found to be associated with shorter survival

and chemotherapeutic resistance (87). TAMs seem to influence CD4+ T-cell dysfunction by preventing access of HRS cells through the PD-1-PD-L1 interaction (87). The combinational use of PD-1 blockade with macrophage depleting therapies such as anti-CSF antibodies or the promotion of inflammatory macrophages through phosphatidyl 3-kinase- γ inhibitors can counteract TAMs

resistance (68).

In lymphoma, we know that tumor vaccines are unable to induce responses, likely due to antigen-TME mismatch (88). One specific target that has emerged in vaccine therapy is the immunoglobulin idiotype (Id) (89). Id peptides can be combined to DNA or protein which causes a DC response *in vivo* (90). Another approach is to load the DNA or protein into DCs. Subsequently, this causes an immune response as DCs generate a specific tumor antigen (90). In one study, 287 patients with untreated FL were randomized 2:1 to 7 months of a protein-based vaccine or placebo after achieving a response (91). The primary endpoint of the study was PFS, and was not significantly different in the two arms at a median follow-up of 58 months, although the PFS among patients who had a humoral response was significantly higher than those who did not. For DC loaded vaccines an Id based protein with tumor lysate was used to illicit an immune response. A group of 18 patients with relapsed indolent B-cell NHL were given a DC-based vaccine with ORR of 33% and 3 CRs (92). An ongoing phase I trial with FL patients examines the use of a personal vaccine with the goal of broad activation of innate and adaptive immunity with nivolumab (NCT03121677). Future approaches related to vaccines will require a better understanding of the TME in order to enhance immunogenicity via novel nanoparticle delivery systems to the tumor-draining lymph nodes (93).

Immunosuppressive metabolites

There are several immunosuppressive metabolites that can contribute to ICI resistance. Adenosine is a molecule that suppresses effector T-cell and increases T regulator (Treg) cells through the A2a receptor (86). Once bound, the receptor enables the tumor proliferation by reducing the activity of DCs, natural killer cells (NKs), M1 macrophages, and CD8+ T-cells (86). In cHL, elevated production and reduced degradation lead to increased adenosine levels and reduced PD-1 blockade (94). Another immunosuppressive metabolite is indoleamine 2,3-dioxygenase 1 (IDO1). IDO1 is an enzyme that converts tryptophan to a metabolite called kynurenine in the TME which causes T-cell anergy and apoptosis (95). This metabolite may be a cause of resistance to ICIs via suppression of T effector cell function. IDO1 inhibitor epacadostat (NCT03322384) is currently being investigated in lymphoma as a synergistic cancer therapeutic agent with ICIs that could overcome immunosuppressive metabolites (96).

Genetic factors

The immune escape that renders ICIs ineffective in certain lymphomas is driven by different genetic and epigenetic factors in the tumor cells and TME. Alteration in the oncogenic and tumor suppressor genes such as phosphate and tensin homolog (*PTEN*), enhancer of zeste homolog 2 (*EZH2*), *MYC* and *TP53* causes immune cell exclusion and suppression (68). As a result, there is decreased expression of the innate immune system. For instance, *PTEN* loss without phosphatidylinositol 3-kinase catalytic subunit (*PIK3CA*) mutations activates the product of class I phosphoinositide 3-kinase (PI3K) in *MCL* (97). *EZH2* inhibits HLA expression in *DLBCL* and *MYC* which cause changes in the transcriptional signatures and mutations in *NF-κB* pathway (98,99). Recent microarray technologies have made the identification of specific genes much easier and allow of analysis of the TME for assessment of immune evasion (100). Epigenetic changes such as DNA methylation and histone post-translational modifications can also cause ICIs resistance (101). In *CLL*, hypomethylations in the promoter region caused *PDL-1* elevations in the protein levels (102). Epigenetic therapies can overcome some of those changes through DNA methyltransferase inhibitors and histone deacetylase inhibitors (103).

Biomarkers of response

There is a need to develop biomarkers that can predict response to ICI therapy in lymphomas. In cHL and PMBL, there is an increased PD-L1/L2 protein expression and it can be indicative of a durable PFS (104). PD-L1 expression is driven by structural variations (SV) on chromosomal PD-L1/L2 loci regions (105). Fluorescence in situ hybridization (FISH) can be used to identify PD-L1 SVs (106). However, in lymphomas beyond cHL and PMBCL, there is no correlation between PD-L1 SVs and response. Tumor immunogenicity is regulated by several complex pathways and immune cells in the TME. Tumor mutational burden (TMB) is considered a biomarker of response in ICI patients. TMB is the total number of nonsynonymous mutations in the tumor (107). In one study, TMB was defined as low when there were less than or equal to 6 mutations per megabase (mt/Mb), intermediate TMB from 7 and 16 mt/Mb, and high with greater than or equal to 17 mt/Mb (108). High levels of TMB in cHL and PCNSL were associated with favorable ORR and PFS (108). TMB expression in *DLBCL*, cHL and PCNSL

tends to be very high while in SLL, PTCL, and NK/T cell lymphoma it is one of the lowest, thereby suggesting that the correlation with TMB may not be linear in lymphomas (109). Other potential biomarkers of ICIs are serum IFN- γ levels and number of CD8-positive monocyte TILs on the tumor sample (110,111). Soluble PD-L1 expression was positively correlated with increased IFN- γ levels and poor prognosis in PTCL (112). PCNSL patients with elevated PD-L1 expression on tissue were also found to have a worse prognosis compared with those with low PD-L1 expression (113). The interplay between ICI use and upregulation of IFN- γ needs further investigation to ascertain subgroups of patients that might benefit from the use of ICIs.

Immune-related adverse events (irAEs) in lymphoma

IrAEs reflect an “over-stimulated” immune system that can affect any body part and most commonly comprise dermatological (rash/dermatitis), gastrointestinal (colitis, hepatitis, pancreatitis), pulmonary (pneumonitis) and endocrine (thyroid, hypophysitis/adrenal crisis) side-effects (114). With anti-CTLA-4 antibodies, irAEs are uncommon but one prevalent treatment related toxicity is diarrhea which occurs in 60% of cases and almost 30% are grade 3-4 (115). In allogeneic HSCT recipients, the use of ipilimumab did not cause any severe GvHD as evidenced in a small trial where 10% of patients developed a grade 3 chronic liver GvHD (116,117). In a large meta-analysis, about 15% of patients treated with PD-1/PD-L1 ICIs were shown to develop irAEs and this increased to 60% in combinational ICI therapy with ipilimumab/nivolumab (118). In a phase I study of r/r NHL (CA209-039) treated with PD-1/PD-L1 antibodies, about 4% of patients developed grade 3-5 pneumonitis (21). One other less severe toxicity was fatigue which was mostly grade 1-2 and occurred in 10-50% of patients (13). In Keynote-089, patients with r/r cHL post AHST received pembrolizumab with common irAEs including hypothyroidism (16%), pneumonitis (5%), and hyperthyroidism (4%) (16). No grade 4 adverse events or treatment-related deaths were reported. Also, in a cohort of 14 patients that received nivolumab for r/r cHL after allogeneic SCT, acute GvHD was found in three patients with a prior history of GvHD (119). The management of irAEs from ICI therapy depends on the particular toxicity, and early recognition and institution of corticosteroids is critical to avoid permanent organ injury or patient mortality. Although corticosteroid

use has been shown to reduce the efficacy of ICI therapy in various solid tumors, this finding has not been replicated in lymphoma studies yet.

Future direction

Although ICI therapy seems to have changed the treatment paradigm for the management of cHL, we have not made many strides with ICI use in other lymphomas. Recently, there is some emerging evidence for potential efficacy of ICI therapy in PMBCL, PCNSL, and cutaneous T-cell lymphomas. Further, there is preliminary evidence of safety and efficacy with ICI use in HIV-associated lymphomas. However, larger studies with longer follow-up are awaited prior to making any practice changing recommendations. Further research is needed to identify the right patient and context of ICI use—either as monotherapy or as combinatorial therapy.

Indeed, ICI therapy has unique advantages and disadvantages compared to other forms of immunotherapy such as CAR-T cell therapy, which has already been approved for certain lymphomas. One obvious positive of ICI therapy is the low rate of severe toxicities, especially when used as monotherapy. Unless in the context of a clinical trial, ICI therapy is typically given to heavily pre-treated patients who have undergone several cytotoxic chemotherapies. ICI therapy presents a well-tolerated approach for these patients. As seen in other malignancies, ICI therapy can also be very practically and safely combined with other anti-cancer agents, and a synergistic effect can be seen due to T-cell immunomodulation when ICI therapy is combined with other targeted or cytotoxic standard therapies (120). ICI therapies also tend to be associated with a durable response possibly, due to the mechanism of revitalizing a host's immune system. Obvious disadvantages to ICI therapy in lymphomas are that they seem to be only effective in certain types of lymphomas. Aggressive lymphomas such as DLBCL and BL often have barriers to ICI effectiveness, due to these tumor's defects in antigen presentation, a low immune cell microenvironment, TAM mediated immunosuppression, and genetic factors.

As aforementioned, with approvals of CAR-T in DLBCL and MCL, there may be value in evaluating the role of ICI use post CAR-T progression as those patients would have altered immune milieu favoring the use of ICI therapies. There are several areas of unmet need in lymphomas, and collaborations between basic scientists and clinical investigators are paramount to harnessing the immune

system effectively and improve patient outcomes.

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