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Checkpoint blockade in Hodgkin and non-Hodgkin lymphoma

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Classical Hodgkin lymphoma (cHL) is characterized by nearly universal genetic alterations in 9p24.1, resulting in constitutive expression of PD-1 ligands. This likely underlies the unique sensitivity of cHL to PD-1 blockade, with response rates of ~70% in relapsed/refractory disease. There are now numerous clinical trials testing PD-1 inhibitors in earlier stages of treatment and in combination with many other therapies. In general, non-Hodgkin lymphomas (NHLs) do not display a high frequency of 9p24.1 alterations and do not share cHL's vulnerability to PD-1 blockade. However, a few entities have genetic or immunologic features that may predict sensitivity to immune checkpoint blockade. These include primary mediastinal B cell lymphoma, primary central nervous system lymphoma, and primary testicular lymphoma, which harbor frequent alterations in 9p24.1, as well as Epstein Barr virus (EBV)–infected lymphomas, where EBV infection leads to increased PD-L1 expression. Although these subtypes may be specifically vulnerable to PD-1 blockade, the majority of NHLs appear to be minimally sensitive to PD-1 blockade monotherapy. Current investigations in NHL are therefore focusing on targeting other checkpoints or studying PD-1–based combination therapy. Looking forward, additional insight into the most common mechanisms of resistance to immune checkpoint inhibitors will be important to guide rational clinical trial design. In this review, we describe the biological basis for checkpoint blockade in cHL and NHL and summarize the clinical data generated to date. Guided by our rapidly evolving understanding of the pathobiology of various lymphoma subtypes, we are hopeful that the role of checkpoint inhibitors in lymphoma treatment will continue to grow.

Introduction

Over the last decade, immunotherapy has become one of the most active areas of investigation in cancer research and has shown therapeutic promise in multiple cancers, leading to the US Food and Drug Administration approval of several novel immunotherapeutic drug classes for both hematologic and solid tumors. Immunotherapeutics generally seek to enhance or manipulate host antitumor immunity. This can be accomplished by many different approaches, including directing a patient's own T cells to react against specific tumor antigens (chimeric antigen receptor [CAR] T-cell therapy), immunization with tumor antigens, enhancing costimulatory signals on immune cells, or disrupting tumors' reliance on checkpoint pathways. Immune checkpoints normally help to downregulate immune responses, but they may be co-opted by a variety of tumors to enhance immune evasion. Therapeutic interference with checkpoint pathways, termed "checkpoint blockade," has enjoyed significant success across many tumor types. Currently, the most widely studied checkpoint is programmed cell death protein 1 (PD-1; CD279), which interacts with its ligands, PD-L1 and PD-L2, on malignant tumor cells, antigen-presenting cells, and T cells.[1] PD-1 and its ligands are members of the CD28-B7 family of receptor–ligand pairs. PD-1 expression is driven by T-cell receptor (TCR) ligation, and expression increases with subsequent TCR triggering. PD-1 ligands, however, are induced by both type I and type II interferon

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signaling, JAK2-mediated cytokines, and Toll-like receptor ligation.[2,3] The interaction between PD-1 and its ligands results in the recruitment of SH2-domain–containing tyrosine phosphatase 2 to the inhibitory motifs present on the cytoplasmic tail of PD-1. This leads to the dephosphorylation of multiple proteins, including components of the TCR signaling complex (CD3ζ and ZAP70), PKCθ, and the phosphatidylinositol 3-kinase–Akt signaling axis. This attenuation of kinase-mediated signaling cascades results in a downstream loss of nuclear factor κB and AP-1 transcription factors and subsequently decreases in cytokine output, including interferon γ and interleukin-2, thus impinging upon effector function and proliferation, respectively.[1] PD-1 signaling can also affect T-cell survival by inhibition of antiapoptotic proteins, such as Bcl-xL,[4] and effector functions through decreases in the T-cell transcription factors Tbet, GATA3, and eomesodermin.[5]

The PD-1/PD-L1 signaling cascade, among others, is important for maintaining peripheral T-cell tolerance during serial TCR triggering events, such as in chronic infections.[6] Illustrating this importance, both PD-1 and PD-L1 null mice are characterized by exaggerated inflammatory reactions in murine models of atherosclerosis, autoimmune encephalomyelitis, sepsis, and cardiomyopathy.[7-9] Numerous tumors also manipulate PD-1 signaling by expressing PD-1 ligands on the tumor cell surface. When PD-1–bearing T cells encounter PD-1 ligands within the tumor microenvironment (TME), a disadvantageous suppression of the endogenous antitumoral T-cell response occurs, leading to tumor preservation and outgrowth. These interactions suggest a dependence on PD-1 signaling and a therapeutic opportunity to restore antitumor immunity.

Herein, we present the scientific rationale and clinical applications of immune checkpoint blockade in classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma (NHL). We focus on the PD-1 synapse, where much of the biological and nearly all of the clinical data are available at present. We also discuss the scientific rationale for combination immunotherapeutic regimens, which may broaden the applicability of checkpoint blockade to a larger subset of lymphomas.

PD-1 blockade in cHL

Biological basis

cHL is a unique tumor with malignant cells making up only a minor fraction of the overall tumor cellularity. These transformed B cells, termed Hodgkin Reed-Sternberg (HRS) cells, are surrounded by a dense, mixed-population inflammatory infiltrate. However, even with the recruitment of so many immune cells to the tumor site, there is an ineffective antitumoral response.[10] In 2010, an amplification block at 9p24.1 was characterized in cHL tumor lines.[11] This area on the short arm of chromosome 9 contains the loci for the *PD-L1* (*CD274*), *PD-L2* (*PDCD1LG2*), and *JAK2* genes and amplification of this region increases PD-1 ligand expression directly at the transcript and protein levels and indirectly through increased *JAK2* expression and increased JAK-STAT signaling. Studies using fluorescence in situ hybridization detected 9p24.1 abnormalities in nearly all tumors collected from a cohort of patients with newly diagnosed cHL, including polysomy (5%), copy-number gain (58%), or amplification (36%) of the *PD-L1* and *PD-L2* loci.[12] At the protein level, it can also be demonstrated that most cHL tumors display increased PD-L1 expression on the cell surface as well as on tumor-infiltrating macrophages.[13] A higher degree of genetic alteration as assessed by fluorescence in situ hybridization correlates with increased PD-L1 protein expression by immunohistochemical staining.[12] Taken together, these studies show that gains of 9p24.1 and PD-1 ligand expression by HRS cells are defining features of cHL.

Altered antigen presentation may also be a biological feature of cHL with high clinical relevance, as it could provide an important mechanism of intrinsic or acquired immune resistance, and might guide the choice of more effective combination therapeutic strategies. Interestingly, HRS cells frequently harbor inactivating mutations in β2-microglobulin that result in reduced or absent β2-microglobulin/major histocompatibility complex (MHC) class I expression on HRS cells.[14,15] The high incidence of attenuated MHC class I expression and the high response rate to PD-1 blockade in cHL suggest that the mechanism of action of PD-1 blockade cannot be restricted to $CD8^+$ T-cell–mediated killing of HRS cells via MHC class I. In contrast, MHC class II is often expressed by HRS cells, and PD-L1 HRS cells are enriched for contacts with $CD4^+$ T cells rather than $CD8^+$ T-cells.[16] These data implicate an important role for $CD4^+$ T cells in mediating antitumor immunity in cHL and suggest additional rational targets such as lymphocyte-activating gene 3 (LAG-3), which negatively regulates $CD4^+$ T-cell responses by binding MHC class II with higher affinity than CD4[17,18] and costimulatory adjuvants such as 4-1BB/CD137 or OX40/CD134 agonists, which eliminate the need for endogenous costimulatory signals for full T-cell activation.[19] In addition, loss of MHC class I expression may make HRS cells more amenable to cell-mediated death by natural killer (NK) cells. To that end, disinhibition of NK cells through blockade of their inhibitory killer cell immunoglobulin-like receptors could help to unleash potent NK-cell–mediated antitumor responses. Tumor-associated macrophages may also play an important role in responses to PD-1 targeted treatments. In cHL, higher rates of tumor-associated macrophages have been associated with primary treatment failure and reduced progression-free survival (PFS).[20] Recent studies show that PD-1 expression on macrophages is associated with a "protumor" M2 state and that blockade of the PD-1 pathway can increase macrophage phagocytosis, decrease tumor volume, and prolong survival in animal models of colon cancer.[21] These findings suggest that combination therapies with other macrophage-targeting agents, like anti-CD47 monoclonal antibodies, may be another attractive clinical strategy. Investigation in this area and others is ongoing and will provide important guidance for future clinical studies.

Clinical experience

Single-agent PD-1 blockade. The high frequency of 9p24.1 alterations and resultant increased expression of PD-1 ligands make cHL a uniquely attractive target for PD-1 blockade. Based on this, the initial phase 1 trials of both nivolumab and pembrolizumab in hematologic malignancies (CHECKMATE 039 and KEYNOTE 013) included independent cohort expansions for patients with cHL. The phase 1 trial of nivolumab demonstrated an investigator-assessed overall response rate (ORR) of 87% and complete response (CR) rate of 17% in 23 patients with heavily pretreated relapsed/refractory (R/R) cHL (Table 1). Responses were durable, with 35% of patients still responding at 1.5 years.[22] The phase 1 study of pembrolizumab reported an independently assessed ORR and CR rate of 65% and 16%, respectively, for 31 heavily pretreated patients with R/R cHL with a median PFS of 11.4 months.[23,24] Building on the promise of these results, registration phase 2 studies were performed. CHECKMATE 205, the phase 2 trial of nivolumab, included 243 patients with R/R cHL, all of whom had relapsed after prior autologous stem cell transplantation (ASCT), and confirmed high response rates (ORR

Table 1. Selected prospective trials of immune checkpoint agents in lymphoma

Agent	Phase/trial name	Clinical setting	No. of patients	ORR, %	CR rate, %	Median PFS
cHL						
Nivolumab[22]	1/CheckMate 039	R/R	23	87	17	Not reached
Nivolumab[25,26]	2/CheckMate 205	R/R	80	68	9	14.8 mo
Pembrolizumab[23,24]	1/KEYNOTE-013	R/R	31	65	16	11.4 mo
Pembrolizumab[27,28]	2/KEYNOTE-087	R/R	210	69	22	Not reached
Nivolumab + ipilimumab[31]	1/CheckMate 039	R/R	31	74	19	Not reached
Nivolumab + brentuximab[32]	1/2	R/R, initial salvage regimen	62	85	63	Not reached
Nivolumab + brentuximab[33]	1	R/R	18	89	50	Not reached
FL						
Pidilizumab + rituximab[58]	2	R/R	32	66	52	18.8 mo
Nivolumab[50]	1	R/R	10	40	10	Not reached
Nivolumab + ipilimumab[31]	1	R/R	5	20	0	Not reached
Atezolizumab + obinatuzumab[53]	2	R/R	26	57	Not reported	Not reached
Pembrolizumab + rituximab[60]	2	R/R	30	80	60	Not reached
Utomilumab + rituximab[61]	1/2	R/R	33	27	12	Not reached
DLBCL						
Pidilizumab + rituximab[52]	2	Consolidation after ASCT	66	51*	34	72% (at 16 mo)
Nivolumab[50]	1	R/R	11	36	18	7 wk
Nivolumab + ipilimumab[31]	1	R/R	10	20	0	Not reached
Atezolizumab + obinatuzumab[53]	2	R/R	23	16	Not reported	Not reached
PMBL						
Pembrolizumab[46]	1/KEYNOTE-013	R/R	18	41	12	Not reached
RT						
Pembrolizumab[51]	1	R/R	9	44	11	5.4 mo
TCL						
Nivolumab[50]	1	R/R	13 MF	15	0	10 wk
			5 PTCL	40	0	14 wk
			5 Other	0	0	7-10 wk
Nivolumab + ipilimumab[31]	1	R/R	7 CTCL	0	0	Not reached
			4 PTCL	25	0	
Pembrolizumab[64]	2	R/R	15 SS	27	7	69% (at 1 y)
			9 MF	55	0	

CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MF, mycosis fungoides; PMBL, primary mediastinal B cell lymphoma; PTCL, peripheral T cell lymphoma; RT, Richter's transformation; SS, Sézary syndrome.
*Among the 35 patients with measurable disease following ASCT.

69%, CR rate 16%) regardless of prior exposure to brentuximab. The median PFS ranged from 12 to 18 months in the trial's 3 different cohorts.[25,26] KEYNOTE 087, the phase 2 trial of pembrolizumab, enrolled 210 patients with R/R Hodgkin lymphoma in 3 separate cohorts, one of which included patients who were ASCT ineligible. Overall, the ORR was 69% and the CR rate was 22%. Notably, all patients with high-risk clinical features (primary refractory disease, resistance to salvage chemotherapy, and lack of response to brentuximab) appeared to benefit from pembrolizumab and had response rates similar to the entire study population.[27,28]

Biomarker studies conducted within the context of the above trials confirmed the underlying biological hypotheses. Indeed, genetic alterations in PD-L1/PD-L2 at 9p24.1 and increased expression of the PD-1 ligands were seen almost universally among cases with available tissue.[22,23,25,27] For example, among the 45 patients with tumor samples in CHECKMATE 205, all had alterations at 9p24.1, including 26 with copy gain and 12 with amplification. PD-L1/ PD-L2 amplification, which had previously been associated with inferior PFS following conventional induction treatment,[12] was linked with higher response quality to nivolumab.[25] Similarly, higher levels of expression of PD-L1 were associated with higher response rates or quality with both nivolumab and pembrolizumab.[25,27]

Importantly, the toxicity profile of nivolumab and pembrolizumab in cHL was similar to that observed in solid malignancies.[29] The most common adverse events in published trials are diarrhea, fever, fatigue, infusion reactions, nausea, pruritus, rash, and hypothyroidism, with low rates (4% to 6%) of drug discontinuation for toxicity.[25,27] Based

Table 2. Ongoing clinical trials of pembrolizumab and nivolumab in cHL

	PD-1 inhibitor	Combination partner	Clinical setting	Phase	No. of patients	Number
First-line therapy	Nivolumab	AVD	Advanced stage	2	51	NCT02181738*
			Early stage unfavorable	2	110	NCT03004833*
			High risk or older advanced stage	1	26	NCT03033914*
	Nivolumab	BV	Ineligible or declined first-line chemotherapy	2	100	NCT01716806*
			Ineligible or declined first-line chemotherapy	2	75	NCT02758717*
R/R trials with BV	Pembrolizumab vs BV		R/R	3	300	NCT02684292*
	Nivolumab + BV vs BV alone		R/R	3	340	NCT03138499*
	Nivolumab	BV	R/R	2	65	NCT03057795*
			R/R	1/2	92	NCT02572167*
			R/R (young patients age 5-30 y)	2	80	NCT02927769*
R/R trials with salvage chemotherapy	Nivolumab	ICE	R/R, before autologous HSCT	2	43	NCT03016871*
	Pembrolizumab			2	40	NCT03077828*
R/R trials with immunomodulatory agents	Nivolumab	Lenalidomide	R/R	1/2	102	NCT03015896
	Pembrolizumab		R/R	1/2	29	NCT02875067
	Nivolumab	Ibrutinib	R/R	2	17	NCT02940301*
	Pembrolizumab		R/R	1	58	NCT02950220
	Pembrolizumab	Acalabrutinib	R/R	2	159	NCT02362035
R/R trials with combined immune checkpoint agents	Nivolumab	Ipilimumab and/or BV	R/R	1	189	NCT01896999*
	Nivolumab	Ipilimumab or lirilumab	R/R	1	375	NCT01592370
	Nivolumab	BMS-986016 (anti–LAG-3)	R/R	1/2	132	NCT02061761
R/R trials in combination with cell-targeted therapies	Pembrolizumab	AFM13 (bispecific anti-CD16/CD30 antibody)	R/R	1	33	NCT02665650*
	Nivolumab	EBV-specific T cells	R/R, EBV positive	1	36	NCT02973113

AVD, doxorubicin, vinblastine, and dacarbazine; BV, brentuximab vedotin; HSCT, hematopoietic stem cell transplantation; ICE, ifosfamide, carboplatin, and etoposide.
*Trial restricted to patients with cHL. Other trials include other malignancies.

on the results of these trials, the US Food and Drug Administration granted accelerated approval for both nivolumab and pembrolizumab in the treatment of R/R cHL, and confirmatory phase 3 trials for each drug are open and recruiting patients (Table 2).

Combination checkpoint blockade. Given the impressive efficacy and tolerability of PD-1 inhibitors in patients with cHL, investigators are testing PD-1 inhibitors in combination with other drugs with the goal of increasing cure rates for initial therapies and achieving deeper and more durable responses for patients with R/R disease. In the upfront setting, trials are combining nivolumab with doxorubicin, vinblastine, and dacarbazine for both early-stage unfavorable-risk (NCT03004833) and advanced-stage cHL (NCT02181738 and NCT03033914). Other trials are testing the combination of nivolumab and brentuximab in the first-line setting for older patients or patients who are ineligible for chemotherapy with advanced-stage cHL (NCT02758717 and NCT01716806).

In the R/R setting, a larger number of combination partners are being tested, including many immune-based treatments. Combination immune checkpoint blockade has been a successful strategy in melanoma,[30] and initial results for dual therapy with nivolumab and ipilimumab were recently reported for 65 patients with advanced hematologic malignancies. Among the 31 patients with cHL, the response rates (ORR 74%, CR 19%) were similar to those seen with PD-1 blockade alone, but grade 3 adverse events were more frequent (29%). Median PFS and duration of response have not yet been reached, and additional follow-up is necessary to determine whether more durable responses could justify the apparent increase in toxicity from dual-checkpoint blockade.[31] Additional clinical trials are testing PD-1 inhibitors in combination with checkpoint inhibitors targeting LAG-3 and killer cell immunoglobulin-like receptor (NCT02061761 and NCT01592370) as well as other immunomodulatory drugs like lenalidomide and ibrutinib (NCT03015896, NCT02875067, NCT02950220, and NCT02940301). Other trials are adding PD-1 blockade to cell-based therapies, like Epstein-Barr virus (EBV)–specific T cells for EBV-positive cHL (NCT02973113).

Combinations with nonimmune treatment partners have also shown encouraging early results. For example, a phase 2 trial is testing the combination of nivolumab and brentuximab as the first salvage therapy for 62 patients with R/R cHL. The overall response rate was 85% (CR 63%), and toxicity was manageable, with 33% of patients experiencing grade 3 adverse events.[32] Another ongoing study of nivolumab and brentuximab also showed encouraging early response rates (ORR 89%, 50% CR) for 18 evaluable patients but reported 2 cases of pneumonitis, including 1 grade 5 event.[33] Additional ongoing trials will be useful in clarifying the safety and long-term efficacy of this combination approach (NCT02684292, NCT03138499, and NCT03057795).

Summary

The above studies provide clear evidence that gains of PD-L1/PD-L2 define a genetic basis for immune evasion in cHL that renders the tumor uniquely sensitive to treatment with PD-1 blockade. However, many questions remain. Several additional checkpoint inhibitors that target the PD-1 pathway at the ligand level (durvalumab, avelumab, and atezolizumab) are in earlier stages of clinical development. Although PD-L1 blockade could augment antibody-dependent cell-mediated cytotoxicity by binding to PD-L1 expressed on HRS cells, its inability to block signaling between PD-1 on infiltrating immune cells and PD-L2 on HRS cells could theoretically impact its effectiveness. The results of ongoing studies will shed light on this balance. Beyond the choice of PD-1 or PD-L1 agent, there are also numerous possible combinations partners and many clinical settings to test them in. Continued collaboration between scientific and clinical investigators and rationally designed clinical trials based on compelling preclinical data will be necessary to determine how to safely and optimally incorporate blockade of the PD-1 pathway into the treatment paradigm for cHL.

PD-1 blockade in NHL

Biological basis

NHLs comprise an incredibly diverse collection of malignancies and, unlike cHL, do not share a common genetically determined sensitivity to checkpoint blockade. Even so, a small number of NHLs appear to have frequent genetic alterations in 9p24.1 with resulting increased expression of PD-L1 and PD-L2. For instance, PMBL, which shares many histologic and genetic features with cHL, has frequent genetic abnormalities at 9p24.1, including amplification and translocations.[11,34-36] In 2013, a study of PMBL tumors showed that 72% expressed PD-L2 and, to a lesser extent, PD-L1 on the cell surface. This expression pattern was restricted to malignant tumor cells and correlated with copy-number gains of *PD-L2* in the malignant cells by quantitative polymerase chain reaction.[34] A subsequent study confirmed the frequent 9p24 deregulation and identified several translocations in PMBL targeting the PD-1 ligand loci.[35] More recently, 9p24.1 copy-number gains and recurrent translocations of these loci have been demonstrated in both primary central nervous system lymphomas (PCNSLs) and primary testicular lymphomas (PTLs). These translocations involve rearrangement of the regulator elements of *TBLX1XR1* and the open reading frame of the PD-L2 gene leading to increased PD-L2 protein expression.[37] In the same series, other translocations involving the superenhancer sequences of the immunoglobulin λ and *PAX5* genes and the regulatory elements of *BCNP1* upstream of the coding sequences for PD-L1 and PD-L2 were also observed. Gray zone lymphoma (GZL) is another rare NHL subtype that appears to have frequent 9p24 amplification.[38] Taken together, these data suggest that PMBL, PCNSL, PTL, and GZL are subtypes of NHL that may share a genetic basis for immune evasion and a potential sensitivity to PD-1 blockade, although none of them display these abnormalities with nearly the same frequency as cHL.

Although 9p24.1 alterations and rearrangements have been reported in other lymphomas, they are rare.[36] Nevertheless, there are other biological mechanisms that support the use of PD-1 blockade in other subtypes of NHLs. Chronic viral infections are a known trigger for increased PD-1 expression and have also been linked with a number of hematologic malignancies. In lymphoma, PD-L1 is indeed inducible by EBV, which is found in tumor cells in a subset of cHLs and DLBCLs.[39] Again, these genetic changes involving PD-L1 translate to increased tumor cell surface expression of the corresponding protein, with high prevalence of overexpression demonstrated in EBV-associated DLBCL and EBV-associated posttransplant lymphoproliferative disorders. In contrast, PD-1 expression on malignant cells is rarely observed in DLBCL not otherwise specified (NOS) (11%) and Burkitt lymphoma (0%).[13]

It is also possible that immune checkpoint expression on tumor-infiltrating lymphocytes (TILs) or other cells within the TME could mediate sensitivity to checkpoint blockade. Unlike HRS cells, FL tumor cells do not typically exhibit gains of 9p24.1 or express PD-1 ligands[40]; however, PD-1 is frequently expressed on TILs in the FL TME. The degree and pattern of expression of PD-1 on TILs has been variably associated with risk of progression and transformation in FL.[41-44] It is likely that the effect of PD-1 signaling has different and even opposing effects on individual T-cell subsets, which may explain the apparently conflicting prognostic value of PD-1–positive T cells and PD-1–positive follicular helper T cells in separate studies.[42,43] Although a greater understanding of the FL TME may help to hone therapeutic strategies in this disease, these results suggest that targeting the PD-1 synapse in FL may still be a worthwhile approach. Coexpression of other immune checkpoints on TILs may be another critical component to immune escape pathways for FL. For example, a recent analysis showed that exhausted FL TILs were characterized by expression of both PD-1 and LAG-3 and that blockade of both PD-1 and LAG3 signaling restored the function of intratumoral $CD8^+$ T cells.[45] It is not yet clear whether checkpoint expression within the TME will predict sensitivity to particular checkpoint inhibitors, but these studies provide a strong rationale for clinical investigation.

Clinical experience

NHLs with frequent 9p24.1 alterations. Based on the frequent genetic abnormalities at 9p24.1 in PMBL, these patients were also included in the phase 1 trials of PD-1 blockade. KEYNOTE 013 enrolled 18 patients with R/R PMBL who were treated with pembrolizumab. Among the 17 evaluable patients, the ORR was 41%, with 2 patients achieving CRs. After a median follow-up of 11.3 months, the median DOR had not yet been reached, and 6 of the 7 responses were ongoing.[46] An international phase 2 study is ongoing to confirm and extend these findings (KEYNOTE-170, NCT02576990). This study should also allow a determination of whether genetic abnormalities correlate with response, which is harder to assess in cHL given the near-universal presence of those abnormalities. As noted above, GZL, an entity which shares overlapping clinical features of DLBCL and cHL, also has frequent 9p24.1 copy-number alterations.[38] A small case series reported CRs in 3 out of 3 patients with mediastinal GZL, all of whom harbored genetic alterations in 9p24.1.[47] Finally, PCNSL and PTL may also be sensitive to PD-1 blockade based on the common 9p24.1 abnormalities in these diseases.[37] Based on this hypothesis, 4 patients with R/R primary CNS lymphoma and 1 patient with a CNS recurrence of primary testicular lymphoma were treated with nivolumab off-trial at 3 institutions. All patients achieved an objective response (including 4 CRs) after a median of only 3 cycles of treatment. Notably, radiologic responses were accompanied by significant improvement in clinical symptoms. At a median follow-up of 17 months, all patients were alive and 3 had ongoing responses.[48] These studies, in addition to the more extensive experience in cHL, suggest that 9p24.1 alterations may be a strong predictor of response to PD-1 blockade, although careful correlative studies in the context of the ongoing phase 2 trials will be required to prove this hypothesis.

DLBCL. Although responses to immune checkpoint inhibitors have been reported in patients with DLBCL NOS, response rates are considerably lower than in subgroups of DLBCL with 9p24.1 alterations. In an initial phase 1 trial of ipilimumab, 1 patient with DLBCL had a durable CR lasting at least 31 months.[49] The ORR among patients with DLBCL in the phase 1 trial of nivolumab was 36% (4/11, 2 CRs); however, half of the responders had remissions lasting <3 months.[50] CHECKMATE 139, an ongoing phase 2 trial of nivolumab in patients with DLBCL NOS, has completed accrual with expected results in 2018. RT is another subset of DLBCL that may be sensitive to PD-1 blockade. A phase 2 trial of pembrolizumab included 9 patients with RT and reported an ORR of 44% (4/9), including 1 CR. The median OS for RT patients was 10.7 months, which compares favorably to historical controls. In biomarker assessments, no patients were found to have copy-number gain at 9p24.1 or positive EBV staining; however, RT patients who responded to pembrolizumab had significantly higher levels of PD-L1 expression.[51] Given these preliminary results, an international study of single-agent pembrolizumab in patients with RT was conducted, which recently ended accrual (NCT02576990 and KEYNOTE-170).

Many clinical trials in DLBCL are attempting to improve response rates and durability of remissions by using the drugs in other treatment settings or in combination. Pidilizumab (a monoclonal antibody directed against PD-1) was tested as a consolidation therapy following ASCT in patients with DLBCL and was associated with a favorable 18-month PFS, including among patients who were positron emission tomography positive after salvage and those with measurable disease after ASCT.[52] However, uncertainty regarding the target of pidilizumab has impeded further clinical development. Other checkpoint inhibitors under active development (pembrolizumab, durvalumab, and combination nivolumab/ipilimumab) are being tested using a similar consolidation strategy after ASCT (Table 3).

In the R/R setting, initial results of checkpoint blockade and CD-20 targeted agents have been discouraging. Among 23 patients with heavily pretreated DLBCL, combined treatment with atezolizumab and obinutuzumab demonstrated an ORR of only 16%.[53] Combined immune checkpoint blockade with nivolumab and ipilimumab was also disappointing, with an ORR of 20% in 10 patients with DLBCL.[31] Trials testing other combinations of immune checkpoint inhibitors like avelumab and utomilumab (NCT02951156) or nivolumab and varilumab (NCT03038672) are ongoing. Investigators are also combining checkpoint inhibitors with immunochemotherapy, radiation, and immunomodulatory agents, like lenalidomide and ibrutinib. Finally, other studies are using checkpoint agents in tandem with or for relapse after CAR T-cell therapy in an attempt to prevent induced exhaustion of the CAR-T product (Table 3).

FL. Given its responsiveness to nonspecific immune agents[54] and allogeneic stem cell transplant[55] as well as occasional spontaneous remissions,[56] FL appears to be an inherently immunosensitive malignancy and therefore an attractive target for treatment with immune checkpoint agents. Initial phase 1 clinical trials of immune checkpoint inhibitors showed occasional, durable responses for patients with FL, including a partial response (PR) to pidilizumab and a CR to ipilimumab.[49,57] In the phase 1 trial of nivolumab, 4 of 10 patients with FL had an objective response (including 1 CR), and, after a median of follow-up of nearly 2 years, 3 of 4 responses were ongoing.[50] CHECKMATE 140, a phase 2 trial of nivolumab in FL, has completed accrual, and results will likely be reported in 2018 (NCT02038946).

Table 3. Selected ongoing trials of immune checkpoint agents in NHL

	Immune checkpoint and drug	Other combination partner	Disease	Clinical setting	Phase	Number of patients	NCT Number
Initial treatment in DLBCL	PD-L1 (avelumab)	RCHOP	DLBCL	Untreated stage II-IV	1	28	NCT03244176
	PD-L1 (durvalumab)	RCHOP or RCHOP + lenalidomide	DLBCL	Untreated	2	120	NCT03003520
Combination checkpoint agents in DLBCL	PD-L1 (avelumab) + 4-1BB (utomilumab)	Rituximab or azacitade or bendamustine	DLBCL	R/R	1b	304	NCT02951156
	PD-1 (nivolumab) + CD27 (varilumab)	NA	DLBCL	R/R	2	106	NCT03038672
DLBCL subtypes with 9p24.1 alterations	PD-L1 (durvalumab)	Lenalidomide	DLBCL subtypes (EBV positive, PCNSL, PTL)	R/R	2	21	NCT03212807
	PD-1 (nivolumab)	NA	PCNSL/PTL	R/R	2	65	NCT02857426
	PD-1 (pembrolizumab)	NA	PCNSL	R/R	2	21	NCT02779101
Combinations including anti-CD20 agents in B-cell NHLs	PD-1 (pembrolizumab)	Rituximab	FL	R/R	2	30	NCT02446457
	PD-L1 (atezolizumab)	Obinutuzumab or tazemetostat	DLBCL or FL	R/R	1	92	NCT02220842
	PD-L1 (atezolizumab)	Polatuzumab vedotin and rituximab or obinutuzumab	DLBCL or FL	R/R	1	92	NCT02729896
	PD-L1 (atezolizumab)	Obinutuzumab and lenalidomide	DLBCL or FL	R/R	1	46	NCT02631577
	PD-L1 (atezolizumab)	Obinutuzumab and bendamustine or obinutuzumab and CHOP	DLBCL or FL	R/R or untreated	1b/2	92	NCT02596971
Other combinations in B-cell NHL	PD-1 (nivolumab)	Brentuximab	CD30+ NHL	R/R	1/2	146	NCT02581631
	PD-1 (pembrolizumab)	Intratumoral G100 (TLR-4 agonist)	FL or MZL	R/R	1/2	65	NCT02501473
	PD-1 (pembrolizumab)	Lenalidomide	Lymphoma	R/R	1/2	29	NCT02875067
	PD-1 (nivolumab)	Lenalidomide	NHL or cHL	R/R	1/2	102	NCT03015896
	PD-1 (pembrolizumab)	Ibrutinib	B cell NHL	R/R	1	58	NCT02950220
	PD-1 (pembrolizumab)	EBRT (20-50 Gy)	NHL	R/R	2	70	NCT03210662
	PD-1 (pembrolizumab)	Dendritic cell therapy, cryoablation	NHL	R/R	1/2	44	NCT03035331
	PD-1 (pembrolizumab)	Entinostat (HDAC inhibitor)	FL or cHL	R/R	2	78	NCT03179930
	PD-1 (pembrolizumab)	Vorinostat (HDAC inhibitor)	cHL, DLBCL, or FL	R/R	1	60	NCT03150329
Combination studies in CLL	PD-1 (pembrolizumab)	Ibrutinib	CLL or MCL	R/R	1/2	40	NCT03153202
	PD-1 (nivolumab)	Ibrutinib	CLL	R/R	2	72	NCT02420912
	PD-L1 (atezolizumab)	Obinutuzumab and ibrutinib	CLL	R/R or high-risk untreated	2	72	NCT02846623
	PD-L1 (durvalumab)	Lenalidomide + rituximab or ibrutinib or bendamustine + rituximab	Lymphoma, CLL	R/R	1/2	253	NCT02733042
	PD-1 (pembrolizumab)	Ibrutinib and fludarabine	CLL	R/R	2	30	NCT03204188
	PD-1 (pembrolizumab)	Ublituximab and TGR-1202 (PI3K δ inhibitor)	CLL or RT	R/R	1/2	12	NCT02535286
	PD-1 (pembrolizumab)	Ibrutinib or idelalisib	CLL or indolent B cell lymphomas	R/R	2	68	NCT02332980
Trials in TCLs	PD-L1 (avelumab)	NA	PTCL	R/R	2	35	NCT03046953
	PD-1 (nivolumab)	NA	PTCL	R/R	2	39	NCT03075553
	ICOS (MEDI-570)	NA	PTCL (follicular variant) or AITL	R/R	1	46	NCT02520791
	PD-L1 (durvalumab)	Lenalidomide	PTCL	R/R	1/2	62	NCT03011814

AITL, angioimmunoblastic T cell lymphoma; CLL, chronic lymphocytic leukemia; EBRT, external beam radiation therapy; HDAC, histone deacetylase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not applicable; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; PI3K, phosphatidylinositol 3-kinase; TLR, Toll-like receptor.

Table 3. (continued)

	Immune checkpoint and drug	Other combination partner	Disease	Clinical setting	Phase	Number of patients	NCT Number
	PD-L1 (durvalumab)	Lenalidomide	NK/T cell lymphoma	R/R	2	22	NCT03054532
	PD-L1 (durvalumab)	Combinations of pralatrexate, romidepsin, and/or azacitadine	PTCL	R/R	1/2	148	NCT03161223
	PD-L1 (durvalumab)	Radiation	CTCL	Untreated or R/R	1	19	NCT03235869
	PD-1 (pembrolizumab)	Decitabine and pralatrexate	PTCL and CTCL	R/R	1	42	NCT03240211
Consolidation after ASCT	PD-1 (nivolumab) + CTLA-4 (ipilimumab)	NA	Lymphoma	Consolidation following ASCT	1/2	42	NCT02681302
	PD-1 (pembrolizumab)	NA	DLBCL, cHL, PTCL	Consolidation following ASCT	2	60	NCT02362997
	PD-L1 (durvalumab)	NA	DLBCL	Consolidation following ASCT	2	46	NCT03241017
Combination with CAR-T cells	PD-L1 (atezolizumab)	KTE-C19	DLBCL	R/R	1/2	31	NCT02926833
	PD-L1 (durvalumab)	JCAR014	DLBCL	R/R	1	42	NCT02706405
	PD-1 (pembrolizumab)	NA	$CD19^+$ DLBCL, MCL, FL	Relapse after anti-CD19 CAR T-cell therapy	1/2	12	NCT02650999

AITL, angioimmunoblastic T cell lymphoma; CLL, chronic lymphocytic leukemia; EBRT, external beam radiation therapy; HDAC, histone deacetylase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not applicable; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; PI3K, phosphatidylinositol 3-kinase; TLR, Toll-like receptor.

Although FL may be responsive to immune checkpoint blockade in some cases, the response rates are significantly lower than for cHL. With the goal of generating synergistic anticancer activity, investigators have begun to combine checkpoint inhibitors with other agents, like anti-CD20 monoclonal antibodies. Preliminary results from several early phase clinical trials suggest that this approach is well tolerated and may be efficacious. A phase 2 trial of pidilizumab in combination with rituximab demonstrated an ORR of 66% and a CR rate of 52%,[58] which compared favorably to historical controls for rituximab alone.[59] In other studies of rituximab-sensitive FL patients, the combination of atezolizumab and obinutuzumab had an ORR of 57%,[53] whereas rituximab and pembrolizumab yielded an ORR of 80%.[60] The combination of rituximab and utomilumab (a 4-1BB agonist) achieved an ORR of 27%, including an ORR of 33% in patients with rituximab-refractory disease.[61] Combination immune checkpoint blockade for FL is also feasible. Preliminary results from a phase 1 study of nivolumab and ipilimumab reported 1 PR among 5 patients with FL but, as mentioned above, noted a potentially higher rate of immune adverse events than with anti–PD-1 monotherapy.[31] Numerous other immune checkpoint combination partners are possible and clinical trials are in planning stages. In addition, ongoing clinical studies in FL are testing checkpoint agents in combination with HDAC inhibitors, radiation, chemoimmunotherapy, or immunomodulatory drugs (Table 3).

TCLs. R/R T-cell lymphomas (TCLs) are a difficult-to-treat, often chemorefractory group of malignancies, yet responses to PD-1 inhibitors have been reported for several subtypes of TCL. A recent retrospective analysis reported the outcomes of 7 patients with NK/T-cell lymphoma, a rare lymphoma that is invariably infected with EBV, who were treated with pembrolizumab. All 7 patients responded to treatment (5 CRs), with 5 patients still responding after a median follow-up of 6 months.[62] Prospective trials of pembrolizumab and durvalumab are ongoing in this disease subgroup (NCT03107962 and NCT03054532). The phase 1 trial of nivolumab included 23 patients with TCLs, including 13 patients with MF and 5 patients with PTCL. Among the cohort of TCLs, the ORR was 17%, including an ORR of 15% for MF and 40% for PTCL.[50] Notably, one patient with a prolonged PR was found to have a rearrangement of *PD-L2* resulting in overexpression of the protein. A study of pembrolizumab in 24 patients with cutaneous TCLs also demonstrated meaningful response rates for patients with MF (5/9, 55%) and Sézary syndrome (4/15, 27%). An additional 9 patients had stable disease and the entire cohort had a 12-month PFS of 69%. Although trials of PD-1 inhibitors in cHL and NHL have largely replicated the toxicity profile seen in solid tumors, 6 out of 15 of patients (40%) with Sézary syndrome developed an immune-mediated skin reaction, which had not been reported previously and may be an important disease-specific toxicity.[63] Additional investigation is necessary to identify the subgroups of patients with TCL who are most likely to respond, and studies are ongoing (Table 2). As with other NHLs, numerous ongoing clinical trials are seeking combination partners for PD-(L)1 inhibitors to improve response rates and achieve deeper remissions. Preliminary results for 11 patients with TCLs from the phase 1 trial of combined nivolumab and ipilimumab did not show a significant improvement in efficacy (ORR 9%) compared with nivolumab monotherapy. Other ongoing trials are testing PD-1 or PD-L1 inhibitors in combination with pralatrexate, romidepsin, azacitadine, and lenalidomide (Table 3).

Summary in NHL

The therapeutic benefit of PD-1 blockade as a single agent is undoubtedly much less in NHL then in cHL. However, select NHL subtypes may be vulnerable, based on genetics or EBV infection for example. In others, it may be hoped that selection of the right combination partners for PD-1 blockade will extend the benefit of checkpoint blockade across a broad spectrum of NHLs. There are dozens of ongoing clinical trials in NHL, in subtypes discussed here as well as in other indolent lymphomas and CLL (Table 3). The great heterogeneity of NHL must be kept in mind when designing trials, making it unlikely that a single therapeutic strategy will be helpful across the entire spectrum. Here again, progress will likely require a deliberate and collaborative approach, building on our rapidly evolving understanding of the molecular pathobiology of various NHL subtypes.

Conclusion

Immunotherapeutics, specifically checkpoint blockade of the PD-1 axis, is an extremely active area of scientific and clinical investigation, and has shown significant therapeutic success in both hematologic and solid tumors. Our rapidly improving understanding of the immune biology of lymphoma has facilitated the recognition of tumors that are uniquely vulnerable to checkpoint blockade, most notably cHL. However, many lymphoma subtypes are not especially sensitive to single-agent checkpoint blockade, and even in cHL, most patients eventually progress on therapy. Optimizing checkpoint blockade in lymphoma is very unlikely to have a uniform answer. However, the successes to date, both in the laboratory and in the clinic, should provide a strong motivation to further our knowledge of the biological basis of checkpoint blockade in lymphoma and continue judicious clinical testing of this strategy. By pursuing the 2 in parallel, we may be best able to choose the optimal target pathways and combination strategies for each tumor type and effectively unleash the power of the immune system across the broad spectrum of lymphoid malignancies.

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Authorship

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