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REVIEW

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New developments in immunotherapy for lymphoma

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ABSTRACT The development of immunotherapies for lymphoma has undergone a revolutionary evolution over the past decades. Since the advent of rituximab as the first successful immunotherapy for B-cell non-Hodgkin lymphoma over two decades ago, a plethora of new immunotherapeutic approaches to treat lymphoma has ensued. Four of the most exciting classes of immunotherapies include: chimeric antigen receptor T-cells, bispecific antibodies, immune checkpoint inhibitors, and vaccines. However, with addition of these novel therapies the appropriate timing of treatment, optimal patient population, duration of therapy, toxicity, and cost must be considered. In this review, we describe the most-promising immunotherapeutic approaches for the treatment of lymphoma in clinical development, specifically focusing on clinical trials performed to date and strategies for improvement.

KEYWORDS CAR-T cells; immune checkpoint blockade; bispecific antibodies

Introduction

The treatment for lymphomas has advanced significantly over the past two decades as multiple new targeted and immunotherapeutic approaches have been developed. However, despite significant improvements in outcomes, 35% of patients with aggressive B-cell non-Hodgkin lymphomas (NHL), 15% of patients with Hodgkin lymphoma (HL), and 60% of patients with aggressive T-cell NHL will have progression of disease after standard frontline therapy[1-3]. For patients with aggressive lymphomas who relapse after initial therapy, a durable response is difficult to achieve with standard salvage therapies alone, due in part to the emergence of drug resistant clones and inability to provide fully planned doses of therapy due to toxicities. As such, new approaches are of continued interest to researchers and clinicians alike[4,5]. Treatment methods using less toxic therapies either as a single agent or in combination, may improve outcomes, with decreased adverse events (AEs) for this needy patient population.

The successful development of immunotherapy for the treatment of lymphomas began with the use of rituximab over 20 years ago. Rituximab is a human/murine, chimeric IgG1 anti-CD20 monoclonal antibody[6]. It revolutionized the treatment of B-cell CD20+ hematologic malignancies, improving overall response rates (ORRs) and survival in both indolent and aggressive B-cell NHL[7-10]. In addition to improving outcomes, the toxicity profile was also found to be very favorable. Rituximab works through antibody cell cytotoxicity (ADCC). Rituximab binds to CD20 on the cell surface and allows for the activation of the complement cascade, direct B-cell lysis, and phagocytosis by macrophages via recognition of complement and Fc receptors. Furthermore, interactions with the FcR also activate natural killer (NK) cells, through ADCC[6]. Given the success of rituximab-based treatments for B-cell NHL, significant efforts toward developing other novel immunotherapies for patients with lymphoma are underway. In this review we will focus on the most recent advances in lymphoma immunotherapy. This will include CAR T cells, bispecific antibodies, immune checkpoint inhibitors, and lymphoma vaccines.

CAR T-cell therapy

CAR T cells are autologous T lymphocytes that have been engineered to express the antigen binding region of an antibody directed against tumor-associated antigens[11]. CAR T cells were originally developed by Zelig Eshhar, when he introduced a CAR into a T cell, repurposing the T cell with new antigen specificity[12]. CAR T cells consist of a recombinant molecule comprising 3 parts: 1) single-chain

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variable domain of an antibody (scFv), 2) a transmembrane domain, and 3) a signal transduction domain of the T-cell receptor (TCR)[13]. The scFv allows for antigen specificity (**Figure 1**). It is created by cloning the variable regions of an antigen specific monoclonal antibody. Cloned DNA plasmids containing either gamma retroviral or lentiviral recombinant vectors are then transfected into target cells[14-16]. Thus far, CD19 has been the most extensively studied target of CAR T-cell therapy for the treatment of lymphoma[17,18].

Upon engaging with a specific antigen, the T cell is activated through the signal transduction domain of the TCR, allowing for T-cell expansion and direct cell cytotoxicity. First-generation CAR T cells used a CD3ζ as the signal transduction domain of the TCR. Thus, T-cell activation was solely dependent on interleukin (IL)-2 production. While this produced excellent tumor-specific killing *in vitro*, there was poor T-cell expansion and anti-tumor activity *in vivo*[19,20]. Inadequate *in vivo* efficacy for first-generation CAR T cells occurred because under physiologic conditions, T cells require interaction with their TCR and multiple co-stimulatory receptors, such as CD28 and 4-1BB[21]. Thus, first generation CAR T cells were limited by a lack of co-stimulation. To improve upon first-generation CAR T cells, second-generation CAR T cells contained a co-stimulatory domain, either CD28 or 4-1BB. With the addition of a co-stimulatory domain, second-generation CAR T cells demonstrated significantly improved *in vivo* cytotoxicity, tumor killing, expansion, and persistence[18,22]. Interestingly the choice of co-stimulatory domains leads to a different functional T-cell subset. In CAR T cells with a CD28 co-stimulatory domain, T-cell expansion and activations is characteristic of effector T cells. While in those designed with a 4-1BB co-stimulatory domain, expanded T cells exhibited characteristics of memory T cells[22-24]. Third-generation CAR T cells were designed with two co-stimulatory domains. The first domain was either CD28 or 4-1BB, and the second domain was CD28, 4-1BB, or OXO40[25-27]. The efficacy and utility of third-generation CAR T cells are currently under investigation. More recently, a fourth-generation of "armored CAR T cells" has been designed to protect T cells from the immunosuppressive tumor microenvironment[28,29]. Armored CAR T cells have been engineered to express cytokines or costimulatory ligands, to help promote T-cell expansion and longevity within the tumor microenvironment[29]. Lastly, CAR T cells have also been generated to recognize multiple antigens. This can either be used to enhance specificity of the target tissue and improve safety; or produce synergistic enhancement of effector functions when both antigens are simultaneously encountered[30,31].

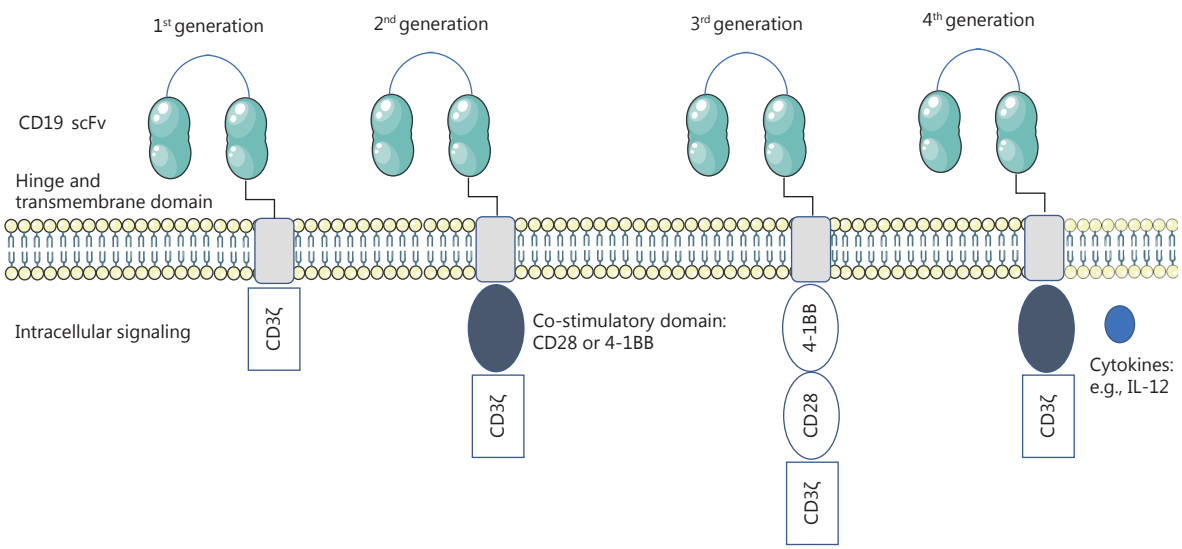

Figure 1 CD19 CAR T-cell structure. A single chain fragment of an anti-CD19 variable region (scFv) is connected to a hinge and transmembrane domain, which is attached to the intracellular signal transduction domain. The 1st generation CD19 CAR T-cells were engineered with CD3ζ as the sole of the signal transduction domain; 2nd generation CD19 CAR T-cells added a co-stimulatory domain, either CD28 or 4-1BB; 3rd generation CD19 CAR T-cells added a second co-stimulatory domain; 4th generation CD19 CAR T-cells have a single co-stimulatory domain, but have been engineered to express cytokines or costimulatory ligands. This figure was created with images adapted from Servier Medical Art by Servier. Original images are licensed under a Creative Commons Attribution 3.0 Unported License.

Clinical application of CAR T cells for the treatment of lymphoma

Thus far, the majority of clinical studies in lymphoid malignancies have used second-generation CAR T cells[32]. To produce clinical-grade CAR T cells, patients must first undergo apheresis of their peripheral blood, where peripheral blood mononuclear cells (PBMC's) are extracted. PBMCs are then transferred to a cell processing facility, where T cells undergo *ex vivo* stimulation and expansion in the presence of CD3 and CD28 magnetic beads[33]. Activated T cells are subsequently transfected using lentiviral or retroviral vectors carrying the CAR construct. The clone is then expanded using CD3/CD28 stimulation. Manufacturing takes approximately 2 weeks[33]. Prior to the infusion of the CAR-T cell product, patients typically receive a preconditioning regimen consisting of cyclophosphamide and fludarabine. This serves to deplete lymphocytes, specifically regulatory T cells, as well as decrease tumor burden, allowing for CAR-T cell expansion[11]. Patients usually require hospital admission for CAR T cell infusions in order to closely monitor for toxicities, especially cytokine release syndrome (CRS) and central nervous system (CNS) toxicity[11].

There have been several collaborations between academic investigators and pharmaceutical companies in the development of CAR T-cell therapies for lymphoma. Investigators at the University of Pennsylvania have collaborated with Novartis to develop a second generation CD19 CAR T-cell product named, CTL019. This construct involves a murine anti-CD19 scFV; a CD8 transmembrane domain, a 4-1BB costimulatory domain, and CD3ζ signal transduction domain[34]. Schuster et al.[34] recently reported the results of initial case series of patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL). In total, 28 of the 38 patients enrolled in the study were treated with CTL019, 14 with FL and 14 with DLBCL (**Table 1**). Fifty-six percent of the patients with FL were double refractory to treatment, and 86% of the patients with DLBCL were also refractory. At 3 months, 64% of the patient had a response. Among patients with DLBCL, ORR was 50%, and FL ORR was 79%. At 6 months, 57% of patients had a complete response (CR):43% for patients with DLBCL, and 71% for patients with FL. Interestingly, 3 patients with FL who had a partial response (PR) at 3 months also had a CR by 6 months. One patient with DLBCL who had a PR at 3 months, had a CR by 6 months[34]. All patients in CR at 6 months remained in remission. After a median follow-up of 28.6 months, 57% of all patients remained progression-free. Among patients with DLBCL, median progression-free survival (PFS) was 3.2 months. Among patients with FL, median PFS was not reached[34]. There was no reported difference in response rate based on DLBCL subtype[34]. Median peak expansion of CTL019 cells in the blood occurred at 8 days in patients who had a response and at 10 days for those who did not. Treatment was overall well tolerated, and toxicities were typically self-limiting. Eighteen percent of patients suffered from grade 3/4 CRS, with only one requiring administration of the anti-IL-6 antibody, tocilizumab. Eleven percent of patients suffered from grade 3/4 CNS toxicity, resulting in one death[34].

In the multi-center, single-arm, open-label, phase 2 JULIET (NCT02445248) trial, patients with R/R DLBCL were treated with CTL019. A recent interim analysis was presented at the 59th annual meeting of the American Society of Hematology. Patients were eligible for the trial if they had progressed after receiving ≥2 lines of chemotherapy, or were ineligible for or had failed autologous stem cell transplant (ASCT)[35]. Of the 81 patients analyzed, the best ORR was 53.1% (95% CI, 42% to 64%; P<0.0001), with 39.5% CR and 13.6% PR. At month 3, the CR rate (CRR) was 32% and the PR rate (PRR) was 6%. Forty-six patients were evaluable for at least 6 months with a durable CRR of 30% and PRR of 7%. Median duration of response (DOR) was not reached; the 6-month probability of being relapse-free was 73.5% (95% CI, 52.0%–86.6%). Median overall survival (OS) was not reached; the 6-month probability of OS was 64.5% (95% CI, 51.5%–74.8%). No patient who achieved a response (CR or PR) proceeded to ASCT or allogeneic stem cell transplant (Allo-SCT). CTL019 was detected in peripheral blood by quantitative PCR for up to 367 days in responders. Overall, 86% of patients had grade 3 or 4 AEs. CRS occurred in 58% of patients, with 23% having grade 3/4 toxicity. Twelve percent of patients suffered from grade 3/4 neurologic toxicity. Fifteen percent of patients required the administration of tocilizumab, and 11% required corticosteroids. Three patients died due to disease progression, while, no deaths were secondary to treatment toxicity[35].

Investigators at the National Cancer Institute (NCI) and KITE Pharmaceuticals developed a second generation CD19 CAR T-cell product named, Axicabtagene Ciloleucel (axi-cel). This construct consists of a single-chain variable fragment extracellular domain targeting CD19 proteins with CD3ζ and a CD28 co-stimulatory domain. In initial early phase studies performed at the NCI, 15 patients with R/R DLBCL, indolent lymphoma, or CLL were treated with a conditioning chemotherapy regimen of cyclophosphamide

Table 1 Summary of key CD19 CAR T-cell clinical trials for the treatment of lymphoma

Study	Phase	Lymphoma subtype	Patients (*n*)	CAR-T product	Efficacy (%)	Safety (%)
Schuster et al.[34]	1/2	R/R	28	CTL019	ORR	3/4 CNS: 11
		DLBCL & FL		2nd generation; 41BB	DLBCL: 43	3/4 CRS: 18
				Lentiviral vector	FL: 71	
Schuster et al.[35]	2	R/R DLBCL	81	CTL019	ORR: 53.1	3/4 CNS: 12
				2nd generation; 41BB	CRR: 39.5	3/4 CRS: 23
				Lentiviral vector		
ZUMA-1[40]	1/2	R/R DLBCL	101	Axi-cel	ORR: 82	3/4 CNS: 28
		PMBCL		2nd generation; CD28	CRR: 58	3/4 CRS: 14
		TFL		Retroviral vector		
Turtle et al.[47]	1	R/R B-cell NHL	32	JCAR014	ORR	3/4 CNS: 28
				2nd generation; 41BB	Cy/Etop conditioning: 50	3/4 CRS: 12.5
				1:1 ratio of $CD4^+$and $CD8^+$ T-cells		
				Retroviral vector	Cy/Flu conditioning: 72	
Abramson et al.[49]	1	R/R DLBCL	74	JCAR017	DL1 ($5*10^7$CAR-T cells)	3/4 CNS: 14
		PMBCL		2nd generation; 41BB	ORR: 40	3/4 CRS: 1
		MCL		Defined ratio of $CD4^+$and $CD8^+$T-cells	CRR: 27	
		FL		Retroviral vector	DL2 ($1*10^8$CAR-T cells)	
					ORR: 63	
					CRR: 58	

and fludarabine followed by a single infusion of anti-CD19 CAR T cells. Of the 15 patients, 8 achieved CR, 4 achieved PRs, 1 had stable disease, and 2 were not evaluable. Responses were durable, ranging from 9 to 22 months. Toxicities including fever, hypotension, and neurologic toxicities occurred, requiring two patients to receive tocilizumab[36-38]. Long term follow-up of responders demonstrated that in 4 of the 5 CRs, the durations of remission were 56, 51, 44, and 38 months; without evidence of relapse. Furthermore, CRs continued after recovery of non-malignant polyclonal B cells in 3 of 4 patients with long-term complete remissions. Lastly, patients had a low incidence of severe infections despite B-cell depletion and hypogammaglobulinemia[38].

ZUMA-1 was a multi-center phase 1 safety, single arm, open-label trial in patients with refractory DLBCL treated with axi-cel. In total, 7 patients were treated. Patients received cyclophosphamide and fludarabine conditioning, followed by axi-cel at a target dose of 2×10^6 CAR T cells/kg. Only 1 patient developed grade 4 CRS/neurotoxicity, with a grade 3/4 CRS incidence of 14% and a grade 3/4 neurotoxicity incidence of 57%. The ORR was 71%, with a CRR of 57%. CAR T cells demonstrated peak expansion within 2 weeks and continued to be detected at greater than twelve months in patients with ongoing CR[39]. Subsequently, a phase 2 treatment portion of ZUMA-1 was opened for patients with refractory DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma[40]. The primary analysis of ZUMA-1 was initially presented at the 2017 American Association of Cancer Research annual meeting[41]. One-hundred and eleven patients were enrolled in the study, with 101 patients receiving axi-cel product. Seventy-seven of the patients had DLBCL, with 24 having either primary mediastinal B-cell lymphoma or transformed follicular lymphoma[40]. At a minimum of 6 months follow-up, the ORR was 82% (95% CI, 73–89), with a 54% CRR. The median time to response was 1 month, with a median DOR of 8.1 months. Response rates were consistent among all clinical and disease specific variables, including IPI score, cell-of-origin subtype, presence of bulky disease, patients

with primary refractory disease, those who had relapsed after auto-transplant, or were treated with either glucocorticoids or tocilizumab[40]. Nine of the 52 patients who had disease progression were retreated, of which 5 had a response. At an updated one-year follow-up analysis of both the phase 1 and 2 portions of ZUMA-1, the objective response rate was 82%, including a CRR of 58%. Interestingly, in 23 of the patients who did not have an initial CR, at a longer follow-up as late as 15 months, they were found to have a CR in the absence of additional treatment. The median DOR was 11.1 months (95% CI, 3.9-could not be estimated). The median duration of PFS was 5.8 months (95% CI, 3.3-could not be estimated), with PFS survival rates of 49% (95% CI, 39–58) at 6 months, 44% (95% CI, 34–53) at 12 months, and 41% (95% CI, 31–50) at 15 months. The median overall survival was not yet reached (95% CI, 12.0 months-could not be estimated), with OS rates of 78% (95% CI, 69–85) at 6 months, 59% (95% CI, 49–68) at 12 months, and 52% (95% CI, 41–62) at 18 months[40].

CAR-T levels peaked in the peripheral blood within 14 days after infusion of axi-cel product and were detectable in most patients at 180 days after infusion, and even up to 24 months. Patients who responded had 5.4 times more expansion of CAR T cells compared to those who did not respond. Peak expansion was significantly associated with neurologic events, but interestingly not with CRS. Elevated levels of IL-6, -10, -15, -2Rα, and granzyme B, were significantly associated with grade 3 or higher neurologic toxicity and CRS. However, elevated levels of IL-2, granulocyte–macrophage colony-stimulating factor, and ferritin, were only associated with neurologic toxicity[40].

The most common grade 3 or higher AEs were neutropenia (in 78%), anemia (in 43%), and thrombocytopenia (in 38%). The incidence of grade 3 or higher febrile neutropenia was 31%. Grade 3 or higher CRS occurred in 13% of patients, while grade 3 or higher CNS toxicity occurred in 28% of patients. 43% of patients received tocilizumab and 27% received glucocorticoids for the management of CRS or CNS toxicity[40]. Results from the ZUMA-1 trial led to the approval of axi-cel by the US Food and Drug Administration (FDA) for treatment of adults with relapsed or refractory DLBCL after 2 or more lines of systemic therapy[42].

Recently, both CD19 and programmed death ligand one (PD-L1) status in baseline and post-progression biopsies of patients who had progressed after treatment with axi-cel were assessed. Twenty-seven percent of patients with CD19-positive lymphoma cells at baseline developed CD19-negative disease at time of disease progression. Furthermore, in ten patients evaluable at the time of disease progression, 80% were PD-L1–positive[43]. These findings, as well as that increased levels of PD-L1 are frequently found in patients with refractory DLBCL, led to the development of the ZUMA-6 trial (NCT02926833); a phase 1/2 single arm trial of axi-cel in combination with atezolizumab (PD-L1 ab) for the treatment of patients with refractory DLBCL[44,45]. Preliminary results from this trial were presented at the 59th annual meeting of the American Society of Hematology. Six patients have thus far been treated without any DLT's observed thus far. The addition of atezolizumab did not result in an increase in CRS, CNS toxicity, or other CAR T cell-related toxicities. The most common grade 3 or higher AE were anemia (67%), encephalopathy (67%), and hyponatremia (50%). The incidences of grade 3 or higher CRS and CNS toxicity was 33% and 67%, respectively. Thus far, five patients have been evaluable for response; with an ORR of 100%, with 1 CR. Interestingly, all patients had a least a 2-fold greater expansion of CAR T cells than those observed in patients enrolled in ZUMA-1[45]. Other ongoing clinical trials exploring axi-cel for the treatment of lymphoma are ZUMA-2 (NCT02601313), a phase 2 multicenter study of axi-cel in subjects with R/R mantle cell lymphoma, and ZUMA-5 (NCT03105336), a phase 2 multicenter study of axi-cel in patients with R/R indolent NHL.

Investigators at Memorial Sloan Kettering Cancer Center (MSKCC), Seattle Children's Research Institute, and Fred Hutchinson Cancer Research Center (FHCRC) formed a venture, Juno Therapeutics, to investigate their CAR T-cell products JCAR014-017. JCAR014 is a CAR T-cell product consisting of a murine anti-CD19 scFV; an IgG4 hinge, a CD28 transmembrane domain; a 4-1BB costimulatory domain; and a CD3ζ signal transduction domain[46]. It is also transfected with a truncated from of the epidermal growth factor receptor, allowing for eradication of the CAR T-cell product[46]. JCAR014 is derived from $CD8^+$ and $CD4^+$ central memory T-cell subsets in a 1:1 ratio[47]. This is in contrast to other CD19 CAR T-cell products which are either derived from unselected T-cells, or one subset alone[47]. In preclinical studies, JCAR014 has been demonstrated to produce enhanced antitumor activity and increased lysis of $CD19^+$ tumors[48]. Researchers at FHCRC performed a phase 1 clinical trial of JCAR014 in patients with R/R B-cell NHL. Thirty-two patients were studied, all receiving cyclophosphamide based lymphodepleting chemotherapy[47]. Eleven patients had DLBCL, 11 patients had histologically transformed DLBCL, 4 patients had mantle cell lymphoma (MCL), and 6 patients had follicular lymphoma (FL). The investigators found that the CAR T-cell expansion and

response rates varied greatly depending on the type of lymphodepleting chemotherapy used. In the 12 patients who received cyclophosphamide (Cy) and etoposide (Etop) lymphodepleting chemotherapy, 90% of patients lost CAR T cells by day 100, with recovery from B-cell aplasia. The ORR for these patients was 50%, with 8 patients developing progressive disease (PD). The remaining 20 patients received Cy and fludarabine (Flu) lymphodepleting chemotherapy. Compared to the patients who received the Cy/Etop lymphodepleting regimen, patients who received Cy/Flu had markedly greater expansion of $CD4^+$ and $CD8^+$ CAR T-cells in the blood in the first 10 days after infusion, and higher numbers of CAR T-cells in the blood 1 and 3 months later. This correlated with an improved ORR of 72%, with enhanced durability of remission in patients who had a CR[47]. The researchers also found that patients who received 2×10^6/kg cell dose had the best response rates, with an ORR of 83%. Severe CRS developed in 12.5% patients, all of whom had received Cy/Flu conditioning. Severe neurotoxicity occurred in 28% of patients and was more frequently seen in patients who received the Cy/Flu preparatory regimen. The highest incidence of severe CRS and neurotoxicity occurred in patients who received 2×10^7 CAR T-cells/kg and Cy/Flu lymphodepleting chemotherapy[47].

Currently, Juno Therapeutics is conducting a multicenter phase 1 trial of JCAR017 in R/R B-cell NHL (NCT02631044). JCAR017 is a CD19-directed CAR T-cell product, with a 4-1BB co-stimulatory domain administered in a defined composition at a precise dose of $CD8^+$ and $CD4^+$ CAR T cells. An interim analysis of the study was recently reported at the 59th annual meeting of the American Society of Hematology. Patients received Cy/Flu lymphodepleting chemotherapy, followed by an infusion of JCAR017 at either of the two dose levels: DL 1, 5×10^7 CAR T-cells; DL 2, 1×10^8 CAR T-cells. Thus far 74 patients have been treated, 69 with DLBCL, 1 FL grade 3B, 1 primary mediastinal B-cell lymphoma (PMBCL), and 5 with MCL. Of the 69 patients in the DLBCL cohort evaluable for safety, 30% had CRS, with 1% grade 4. Twenty percent had neurotoxicity, with 14% having grade 3/4 neurotoxicity. Nineteen percent of patients were treated with tocilizumab, steroids, or both. Sixty-eight patients thus far have been evaluable for response. The best overall, 3-month, and 6-month response rates were 75%, 49%, and 40%, respectively. The best overall, 3-month, and 6-month CRRs were 56%, 40%, and 37% respectively. It appears there are improved response rates at 3 months in patients treated at DL 2 compared to DL1, with ORR of 63% (95% CI; 38–84) *vs.* 40% (95% CI; 23–59); $P = 0.148$, and a CRR of 58% (95% CI; 34–80) *vs.* 27% (95% CI; 12–46); $P = 0.0385$. In subgroup analysis among patients with double or triple hit lymphoma, the best ORR was 81%, and 3-month CRR was 60%[49].

Correlative analysis from pre- and post-treatment biopsy samples were analyzed to assess for clinical efficacy. Patients who had a CR or PR at 3 months appeared to have a higher percentage of endogenous $CD4^+$ cells in pretreatment tumors than those with PD (CR, PR median: 7.9%; PD median: 0.38%; $P<0.0001$). The level of CAR T-cell tumor infiltration trended higher in patients achieving a CR (median: 3.9%) or PR (median: 1.1%) compared to those with a SD or PD (median: 0.51). Patients who achieved a CR had a higher ratio of CAR T-cells that were $CD8^+$ compared to $CD4^+$, than those with SD or PD (CR median: 0.83; SD/PD median: 0.14; $P = 0.0097$). Similarly, achieving a CR or PR trended toward having an increased infiltration of $CD8^+$ T-cells in tumors as compared to patients achieving SD or PD (CR, PR median change: +5.3%; SD, PD median change: +0.06%; $P = 0.1225$). Lastly, increases in $CD8^+$ T-cell infiltration was associated with increases in indoleamine-pyrrole 2, 3-dioxygenase and PD-L1 expression[50].

Investigators also found that pre-CAR T-cell infusion biomarkers associated with the occurrence of neurotoxicity were higher serum LDH, ferritin, CRP, IL-6, IL-8, IL-10, TNF-α, IFN-α2, MCP-1, and MIP-1β ($P<0.05$ for each). Higher pre-CAR T-cell infusion plasma IL-8, IL-10, and CXCL10 were specifically associated with increased grade 3/4 neurotoxicity ($P<0.05$). Furthermore, investigators discovered that higher ECOG scores and transformed DLBCL correlated with lower durable response at 3 months ($P = 0.02$). Pre-CAR T-cell infusion correlates associated with best ORR included lower ferritin, LDH, CXCL10, G-CSF, and IL-10. Correlates associated with durable response at 3 months included lower ferritin, CRP, LDH, CXCL10, IL-8, IL-10, IL-15, MCP-1, MIP-1β, TNF-α, and higher pre-CAR T-cell infusion, hemoglobin and albumin ($P<0.05$)[51].

CAR T-cell therapies have shown great promise and are now starting to be used to treat patients with lymphoma outside of clinical trials. However, questions remain in optimizing their use. First, determining the mechanisms of resistance and how they can be overcome are yet to be fully elucidated. Furthermore, optimization of conditioning regimens, as well as potentially combining CAR T-cell therapies with other immunotherapeutic approaches (i.e. checkpoint inhibitors), will likely improve efficacy. The optimal timing for CAR-T cell therapy will need to be explored as well. Currently, CAR T-cell therapies have only been studied in patients with R/R disease, typically after failing ASCT. However, studies will need to be performed to

determine the optimal sequence of treatment. If CAR T-cell therapy is found to be more efficacious than ASCT, this will have significant implications when it comes to the cost of patient care. Lastly, how to design targets specific for other lymphoma subtypes is still currently in development. Targets that are actively being studied include CD20, CD22, CD30, and CD79a.

Bispecific antibodies

Bispecific antibodies (BsAb) are rationally designed antibodies that specifically redirect T-cells to a target antigen[52]. In the setting of tumor immunotherapy, T-cells are directed against a specific tumor antigen. The first BsAb was generated in the 1986 by Staerz et al.[53,54]. Since then there has been significant progress in the development of BsAbs, and now several different classes have been designed. BsAbs are engineered by combining scFv domains of two different antibodies with a polypeptide linker chain. One scFv domain recognizes CD3ζ on T-cells, while the other scFv binds tumor associated antigens[52]. This allows the antibody to target surrounding T cells to specific antigen-expressing tumor cells. Thus, T-cell activation is exclusively dependent on the interaction between tumor-associated antigens and CD3ζ, and independent of MHC complex and antigen specificity required to activate naive T-cells[55].

The design of BsAbs can be divided into whether an Fc domain has been incorporated. We will focus on those without Fc domains, as they are the most developed and currently in clinical practice. One design that has been successful in both preclinical and clinical investigation are bispecific T-cell engagers (BiTes). BiTes are comprised of one single-chain variable fragments specific for CD3, and one for a tumor specific antigen (**Figure 2**)[52]. Blinatumomab, is a CD19 specific BiTe, that has demonstrated notable clinical benefit in CD19+ B-cell malignancies, specifically ALL, resulting in its FDA approval in 2014. Blinatumomab has been studied in a phase 1 open label dose escalation clinical trial in patients with R/R NHL[56]. Seventy-six patients were enrolled, 24 with FL, 28 with MCL, and 14 with DLBCL. The maximum tolerated dose (MTD) of blinatumomab was found to be 60 μg/m^2/day on day 1. At the MTD, the ORR was 69%, with 37% CRR. The ORR was higher in indolent lymphoma (FL, ORR 80%; MCL, ORR 71%; DLBCL, ORR 55%). The median DOR at the MTD, was 13.5 months. The most common grade 3/4 AEs were hematologic, with 79% developing lymphopenia, 17% neutropenia, and 12% thrombocytopenia. Twenty-two percent of patients developed grade 3 neurotoxicity[56]. In a phase 2 study of patients with R/R DLBCL, the efficacy and safety of blinatumomab was assessed using different dosing schemes[57]. The investigators used a Simon 2-stage design, where patients either received continuous blinatumomab as a dose escalation to a target dose of 112 μg/d, or a flat fixed dose of 112 μg/d. They found that when using the flat dosing scheme, the incidence of neurotoxicity was too high. Subsequently, all but two patients were treated with a dose escalation strategy. The ORR was 43%, with a CRR of 19%. The median DOR

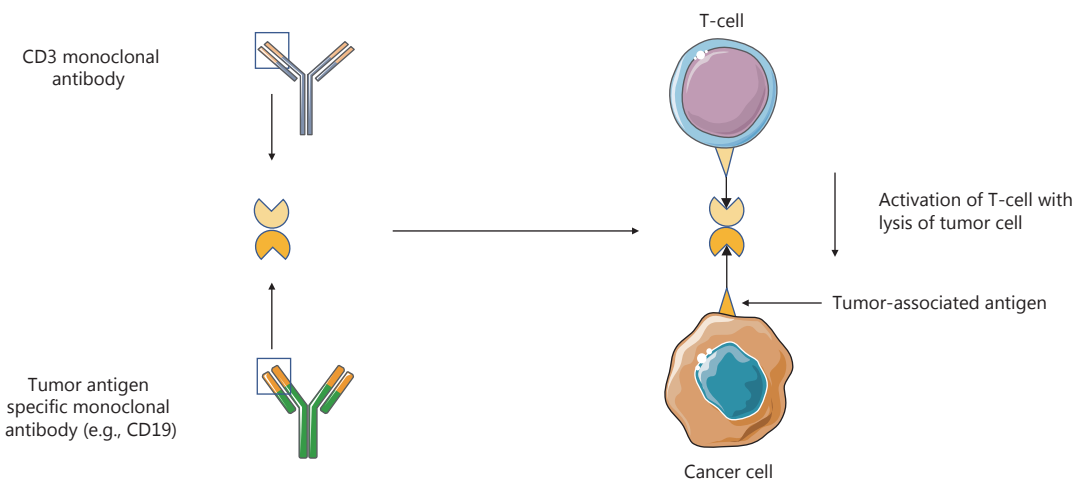

Figure 2 Bispecific T-cell engager design (BiTE). BiTEs consist of two single-chain variable fragments (scFv) of monoclonal antibodies joined by a linker. One scFv domain recognizes CD3ζ on T-cells, while the other scFv binds tumor specific antigens. The scFv of the antibody targets surround T-cells to specific antigen-expressing tumor cells, allowing for T-cell activation to occur exclusively between tumor-associated antigens and CD3ζ. This figure was created with images adapted from Servier Medical Art by Servier. Original images are licensed under a Creative Commons Attribution 3.0 Unported License.

was 11.6 months (95% CI; 0.9-not estimable). The median PFS was 3.7 months (95% CI; 1.4–7.7), and the median OS was 5.0 months (95% CI; 2.3-not estimable). The most common grade 3/4 hematologic AEs were leukopenia (17%) and thrombocytopenia (17%). Twenty-two percent of patients developed grade 3/4 neurotoxicity[57]. There are currently several clinical trials investigating blinatumomab for patients with lymphoma. These studies include combining blinatumomab with chemotherapy for relapsed lymphoma (NCT02568553), assessing the efficacy of blinatumomab in patients with DLBCL who have minimal residual disease status after auto-transplant, (NCT03298412), and investigating a subcutaneous formulation in patients with indolent lymphoma (NCT02961881).

FBTA05 (Lymphomun) is a trifunctional heterodimeric BsAb that recognized both CD20 and CD3. Ten pediatric patients with R/R B-cell malignancies were treated with escalating dosing of FBTA05. Of these 10 patients, 3 had DLBCL. The patients with DLBCL, received daily FBTA05 after receiving debulking chemotherapy. One patient developed a CR, 1 had a PR, and 1 had SD[58]. A chemically crosslinked CD20/CD3 BsAb has also been evaluated in clinical trials[59,60]. In two separate clinical trials, patients with R/R NHL were treated with CD3/CD20 BsAb in combination with an infusion of activated T-cells following ASCT. In one of the trials patients also received concomitant IL-2 infusions. While efficacy was difficult to assess in the setting of ASCT, the infusions were found to be safe, and produced endogenous cytotoxic responses against lymphoma targets[59,60].

For BsABs, studies are just starting to assess their efficacy for the treatment of patients with lymphoma. Unlike CAR T cells, the immediate availability of the drugs, the ability to stop the drug if side effects arise, and decreased likelihood of developing long-term side effects make treatment with BsABs very appealing. Future studies will need to focus on determining the best treatment setting for their use, either as part of induction *vs*. consolidation *vs*. relapse. Other potential targets are also being investigated including CD20 and CD30[52]. Furthermore, continued improvements in antibody structure, as well as combination with other immunotherapies may improve efficacy. One such approach has been to genetically modify tumor or effector immune cells to express BsABs or cytokines, to help overcome the immunosuppressive tumor microenvironment[52].

Checkpoint inhibitors

Immune checkpoints refer to the inhibitory pathways of the immune system that are critical for maintaining self-tolerance. Thus, they help regulate the duration and magnitude of physiological immune responses to promote immune tolerance and minimize tissue damage[61]. Over the past two decades research has demonstrated that tumors are able to exploit immune checkpoints, as a mechanism of immune resistance and tumor escape[61]. Specifically, expression of immune checkpoint ligands and receptors has been found to be potent inhibitors of T-cell tumor immune surveillance and immunity[62]. T-cell activation requires two steps. The primary signal is between the TCR and antigen bound to the MHC complex of the antigen presenting cell (APC). The second signal is co-stimulation, whereby a co-stimulatory receptor on the T-cell will interact with a ligand on the APC. However, co-inhibitory signaling also occurs, where the receptor-ligand interaction will result in inhibition of the T-cell response. The most well studied stimulatory ligands-receptors include CD28 with B7 ligands CD80 and CD86[63]. The most well studied co-inhibitory ligands-receptors include cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and its ligand PD-L1[63,64]. In general, inhibitory receptors and ligands that regulate T-cell effector functions are frequently overexpressed on tumor cells within the tumor microenvironment, as opposed to activating receptors and ligands which are generally not overexpressed on tumor cells. CTLA-4 expression primarily occurs in lymph nodes. Conversely, PD-1 overexpression primarily occurs within the tumor microenvironment, inhibiting T-cell anti-tumor immunity[61].

CTLA-4 was the first immune-checkpoint receptor to be clinically targeted. It is expressed primarily on T cells where it controls the initial stages of T-cell activation. Principally, CTLA-4 opposes the action of the T-cell co-stimulatory receptor, CD28[65]. Once the TCR engages with antigen, CD28 amplifies TCR signaling to activate T-cells. CD28 and CTLA-4 share ligands: CD80 and CD86[66,67]. CTLA-4 appears to have an increased binding for both ligands, and thus decreases the activation of T-cells by outcompeting CD28 for the binding of CD80 and CD86. This leads to active inhibition of T-cells, with the delivery of inhibitory intracellular signaling[68,69]. The critical role of CTLA-4 as a negative regulator of T-cells was demonstrated in a CTLA-4 knockout mouse model, in which mice developed lethal systemic immune hyperactivation[70,71]. While CTLA-4 is expressed on $CD8^+$ T-cells, the major physiological role appears to occur through its effects on $CD4^+$ T-cells. Specifically, CTLA-4 blockade results in an augmented immune response that is dependent on helper T-cells, while CTLA-4 interaction with regulatory T-cells (Treg) boosts

their suppressive function[72]. Therefore, clinical blockade of CTLA-4 results in both the enhancement of $CD4^+$ helper T-cell activity, and inhibition of Treg cell immunosuppression[72].

The primary function of the PD-1/PD-L1 co-inhibitory axis is to limit the activation of T- cells in peripheral tissues in response to infection, and to limit autoimmunity[73,74]. PD-1 expression is induced on the surface of activated T-cells. The two ligands for PD-1 are PD-L1 and programmed cell death ligand 2 (PD-L2)[75,76]. Similar to CTLA-4, PD-1 is highly expressed on Tregs, allowing for enhanced proliferation upon engagement with PD-L1[77]. Tumors are highly infiltrated with Tregs that suppress effector immune response. Thus, within the tumor microenvironment this has allowed for a major mechanism of immune escape and resistance[78]. Blockade of the PD-1/PD-L1 axis may also augment antitumor immune responses by decreasing the activity of intra-tumoral Tregs.

PD-1 is also induced on other activated non-T-cell lymphocytes, including NK cells and B-cells. Overexpression of PD-1 on these lymphocytes also inhibits their anti-tumor activity[79]. Thus, inhibition of the PD-1/PD-L1 axis may also enhance NK cell tumor immunity and may improve antibody production against tumors by B-cells. Lastly, chronic antigen exposure, either during chronic viral infection or malignancy, can lead to high levels of persistent PD-1 expression, inducing a state of exhaustion among antigen-specific T-cells. T-cell exhaustion appears to be partially reversed by PD-1 blockade[80].

Clinical application of immune checkpoint inhibitors in the treatment of lymphoma

Mutations affecting the PD-1 and PD-L1 pathways have been found in both HL and NHL. However, the response to immune checkpoint blockade varies greatly between different subtypes of lymphoma, likely reflecting the variable expression and resistance pattern of immune checkpoints[44]. Furthermore, lymphomas associated with EBV infection are associated with very high levels of PD-L1 expression, as well as high expression of PD-1 on tumor infiltrating lymphocytes[81]. This is consistent in both HL and DLBCL, where EBV infection appears to increase PD-L1 promotor activity and subsequent expression on tumor cells[82,83]. Moreover, several lymphomas have been found to have a high presence of genetic aberrations at the 9p24 gene locus, the location of the PD-L1 and PD-L2 genes. Specifically, in PMBCL studies have demonstrated gains or amplifications at the 9p24 locus in up to 70% of cases[84,85]. While in classical HL (cHL) up to 97% of cases will have alterations at the 9p24 locus[86]. In EBV- primary CNS lymphoma and primary testicular lymphoma, greater than 50% of cases will have 9p24.1 copy gain and increased expression[87]. Lastly, in EBV driven natural killer/T-cell lymphomas (NKTCL), expression of PD-L1 is high on tumor cells secondary to upregulation of the MAPK/NF-κB pathway. High serum soluble PD-L1 (≥3.4 ng/mL) or a high percentage of PD-L1 expression in tumor specimens (≥38%) was associated with poor CRR and OS[88]. In the next sections we will review the results of clinical trials for checkpoint inhibitors in patients with lymphoma.

HL

HL is thought to be the ideal disease subtype for checkpoint inhibitors given its underlying pathophysiology. As previously mentioned, there are almost uniform alterations present at the 9p24 locus[85]. However, the tumor microenvironment, which is rich in inflammatory tumor infiltrating lymphocytes with rare lymphoma cells, also makes it an attractive disease target for checkpoint blockade[89]. Nivolumab, a human IgG4 anti-PD-1 monoclonal antibody, was first studied in heavily pretreated HL patients in the phase 1 CheckMate-039 trial (**Table 2**). Twenty-three patients were enrolled in the study; 78% had already underwent ASCT or had received salvage treatment with brentuximab vedotin (BV). The MTD was not determined, but the highest dose cohort at 3 mg/kg was well tolerated. Grade 3 drug related AEs occurred in 22% of patients. The ORR was 87% (95% CI; 66–97), including 17% with CR and 70% with PR. The PFS at 24 weeks was 86%[90]. This was followed by CheckMate-205, a multicenter phase 2 prospective study of nivolumab dosed (3 mg/kg every two weeks) for patients with R/R HL after treatment with both ASCT and BV. Eighty patients were enrolled in the study, and at a median follow-up of 8.9 months, the ORR was 66.3% (95% CI; 54.8–76.4), with a CRR of 7%. The most common drug-related grade 3/4 AEs were neutropenia and elevated lipase in 5% of patients each. Correlative analysis of pretreatment biopsies in 10 patients revealed overexpression or increases in copy number in PD-L1 and PD-L2 in all 10 sampled biopsies[91]. Based on this study, nivolumab was granted accelerated approval by FDA in May 2016 for the treatment of patients with HL who had relapsed or progressed despite ASCT and BV[92].

Pembrolizumab is a humanized IgG4 anti-PD-1 monoclonal antibody. In the phase 1b keynote-013 trial in patients with relapsed hematologic malignancies, pembrolizumab was administered intravenously at a dose of 10 mg/kg every 2 weeks. Of this study population 31 patients

Table 2 Summary of key checkpoint inhibitor clinical trials for the treatment of lymphoma

Study	Phase	Lymphoma subtype	Study agent	Patients (*n*)	Efficacy (%)
HL					
Checkmate-039[90]	1	R/R HL	Nivolumab	23	ORR: 87
					CRR: 17
					PFS at 24 weeks: 80
Checkmate-205[91]	2	R/R HL	Nivolumab	80	ORR: 66.3
					CRR: 7
Keynote-013[93]	1	R/R HL	Pembrolizumab	31	ORR: 65
					CRR: 16
					PFS at 24 weeks: 69
Keynote-087[94]	2	R/R HL	Pembrolizumab	210	ORR: 69
					CRR: 22.4
					PFS at 6 months 72.4
Herrera et al.[95]	1/2	R/R HL	Nivolumab + brentuximab vedotin	62	ORR: 85
					CRR: 62
Diefenbach et al.[96]	1	R/R HL	Ipilumumab + brentuximab vedotin	12	ORR: 67
					CRR: 42
B-cell NHL					
Keynote-013[98]	1b	R/R PMBCL	Pembrolizumab	21	ORR: 50
					CRR: 25
Keynote-170[99]	2	R/R PMBCL	Pembrolizumab	49	ORR: 41
					CRR: 14
Checkmate-039[100]	1	DLBCL, FL, and other B-cell NHLs	Nivolumab	31	DLBCL
					ORR: 36
					CRR: 18
					FL
					ORR: 40
					CRR: 10
					B-cell NHL
					ORR: 0
Checkmate-039[101]	1	DLBCL and FL	Ipilimumab + nivolumab	15	ORR: 9
					CRR: 0
T-cell NHL					
Checkmate-039[100]	1	MF,	Nivolumab	23	MF
		PTCL, sézary syndrome CTCL, and other CTCL			ORR: 15

Continued

Continued

Study	Phase	Lymphoma subtype	Study agent	Patients (*n*)	Efficacy (%)
					CRR: 0
					PTCL
					ORR: 40
					CRR: 0
					Sézary syndrome CTCL, and other CTCL
					ORR: 0
Khodadoust et al.[104]	1	CTCL	Pembrolizumab	24	ORR: 38
					CRR: 3.6

had R/R HL. All patients had previously received BV, and 71% had undergone ASCT. Sixteen percent of patients developed grade 3 treatment-related colitis, increased ALT and AST levels, nephrotic syndrome, joint swelling, back pain, and axillary pain. The ORR for the cohort was 65% (90% CI; 48–79), with 16% of patients achieving a CR. Responses were durable, with 70% of patients who achieved a response, having a DOR $\geq$ 24 week (range, 0.14 to 74 weeks). The PFS and OS rates at 24 weeks were 69% and 100%, respectively. Correlative studies demonstrated increased levels of PD-L1 and PD-L2 in Reed-Sternberg cells by immunohistochemistry (IHC) in biopsied samples. Furthermore, treatment with pembrolizumab resulted in a significant increase in the absolute number of T cells, $CD4^+$ and $CD8^+$ T-cell subsets, and NK cells in patients' peripheral blood samples. Lastly, treatment with pembrolizumab led to increased activation of expanded immune-related signaling pathways[93]. This lead to the phase 2 keynote-087, a single-arm study of pembrolizumab in 3 patient cohorts: (1) those who had received ASCT and BV; (2) those who were treated with salvage chemotherapy and BV, and who were ineligible for ASCT; and (3) patients who received ASCT, without BV. Pembrolizumab was administered at 200 mg intravenously every 3 weeks. In total, 210 patients were enrolled in the trial, with close to equal distribution between cohorts. The ORR across all cohorts was 69.0% (95% CI; 62.3–75.2) and the CRR was 22.4% (95% CI; 16.9–28.6). The ORR was 73.9% (95% CI; 61.9–83.7) for cohort 1, 64.2% (95% CI; 52.8–74.6) for cohort 2, and 70.0% (95% CI; 56.8–81.2) for cohort 3, which was not statistically different from one another. ORR was similar for patients who had received less than *vs.* greater than 3 previous lines of therapy: 71.4% *vs.* 68.7%. At 6 months, the PFS was 72.4%, while the OS was 99.5%. Furthermore, 75.6% of patients had a DOR greater than 6 months. Over 90% of patients had high intensity staining for PD-L1 in Reed-Sternberg cells[94]. This lead to accelerated FDA approval to pembrolizumab for the treatment of patients with refractory cHL, or those who have relapsed after 3 or more prior lines of therapy in March of 2017.

Recently, the novel combination of nivolumab plus BV was studied in patients with R/R cHL. The study was designed in 21-day cycles for up to 4 cycles. BV was administered at a dose of 1.8 mg/kg on cycle 1, day 1, and nivolumab was administered at a dose of 3 mg/kg on cycle 1, day 8, and day 1 of cycles 2–4. Sixty-two patients were enrolled in the study, with 58 completing all 4 cycles of therapy. The incidence of grade 3/4 immune-related AEs (IRAE's) was 13%, with 5% of patients requiring the use of corticosteroids. Infusion-related reactions occurred in 41% of patients. The ORR was 85% with a CRR of 62%. Sixty-five percent of patients initiated ASCT, and all patients were able to have stem cells collected. Peripheral blood immunophenotyping revealed an increase in pro-inflammatory cytokines and chemokines after treatment with BV. There was a reduction in Tregs after administration of BV, with a subsequent increase in T-cell subsets after combination treatment. Lastly, T-cell expansion was also observed after combination therapy[95].

Ipilimumab is a human IgG1 anti-CTLA-4 monoclonal antibody that was investigated in combination with BV in patients with R/R cHL. In the phase 1 E4412 Eastern Cooperative Oncology Group-Acrin study, patients were initially treated with BV (1.8 mg/kg) and two escalating doses of ipilimumab (1 mg/kg or 3 mg/kg). The 3 mg/kg dose was deemed safe and therefore a subsequent cohort was treated at the higher dose level. Patients received BV every 3 weeks for up to 16 cycles and ipilimumab every 3 weeks $\times$ 4 doses and then every 3 months for up to a year. The incidence of grade 3/4 toxicity was low, with one patient each developing rash, vomiting, peripheral sensory neuropathy, and

thrombocytopenia. At the interim analysis of the 12 evaluable patients, the ORR was 67% with a CRR of 42%. With a median follow-up of 0.66 years, the median PFS was 0.74 years[96].

Currently there are several trials investigating the role of checkpoint inhibitors as part of front line therapy either as a single agent (NCT03331731) or in combination with conventional chemotherapy (NCT03331341 & NCT 03004833). It is also being studied as consolidation after front line treatment for high risk patients (NCT03033914). In the relapsed setting, checkpoint inhibitors are being compared head to head against BV (NCT02684292), as well as in combination with targeted agents such as ibrutinib (NCT02940301).

B-cell NHL

While efficacy and response rates to checkpoint inhibitors in HL have been very encouraging, in NHL clinical efficacy has been more modest. Ipilimumab was studied in 18 patients with R/R B-cell NHL. Patients were treated with ipilimumab at 3 mg/kg once and then monthly at either at 1 mg/kg × 3 months, with subsequent escalation to 3 mg/kg monthly × 4 months. Only two patients had responses; one CR in a patient with DLBCL and one PR in a patient with FL. However, responses were durable[97]. Given the frequent alterations at 9p24 locus in patients with PMBCL, keynote-013, a phase 1b trial in patients with R/R PMBCL, was initiated where patients were first treated with pembrolizumab 10 mg/kg every 2 weeks, but later changed to 200 mg every 3 weeks for up to 2 years. The most recent interim analysis was presented at the 14th International Conference on Malignant Lymphoma Palazzo dei Congress[98]. Twenty-one patients thus far have been treated. At a median follow-up duration of 14.3 months, only 4 patients experienced grade 3/4 treatment-related AEs, with neutropenia being most common (3/4 patients). Nineteen of the 21 patients were evaluable for response, with an ORR of 50% and CRR of 25%. Median DOR was not reached (range, 1.4 to 28.9 months); but DOR in patients with CR ranged from 1.4 to 27.1 months[98]. This has led to a multicenter phase 2 trial (Keynote-170) of pembrolizumab in patients with R/R PMBCL. At the most recent interim analysis, 49 patients have been treated. Presently, the ORR has been 41%, with a CRR of 14%. Of the patients who responded, 76% were positive for PD-L1, 3% were PD-L1 negative, and 21% had unknown PD-L1 status. At 12 months, 62% of patients were alive[99].

Nivolumab has also been studied in patients with B-Cell NHL as part of the Checkmate-039 trial[100]. In this phase 1, open-label, dose-escalation trial, 31/81 patients had B-cell NHL (11 DLBCL, 10 FL, 10 other). Patients received nivolumab at doses of 1 or 3 mg/kg every 2 weeks for up to two years. Twenty-six percent of patients with B-cell NHL suffered grade 3/4 AEs, with the most common being pneumonitis. For patients with DLBCL the ORR was 36%, with a CRR of 18%. Median PFS was 7 weeks (95% CI; 6–29). For FL, the ORR was 40%, with a CRR of 10%. The median PFS was NR (95% CI; 7–NR). For other B-cell NHLs, there was no objective responses. Correlative studies revealed that PD-L1 expression was present on nonmalignant cells within the tumor microenvironment, and less frequently on tumor cells[100]. As part of the Checkmate-039 trial, a cohort of patients received combination of ipilimumab + nivolumab. In total, 65 patients with R/R HL, B-cell NHL, T-cell NHL, and multiple myeloma were treated. Overall, the combination was well tolerated, however there was not a significant improvement in response rates with combination therapy compared to single agent nivolumab[101].

Currently, there are several trials investigating the role of checkpoint inhibitors in combination with rituximab (NCT02446457 & NCT03245021), in combination with chemoimmunotherapy (NCT02541565, NCT03259529, and NCT03366272), or in combination with lenalidomide (NCT03015896 and NCT02631577). Preliminary results from these novel treatment approaches are encouraging, demonstrating improved response rates[102,103].

T-cell NHL

Pembrolizumab has been studied in patients with R/R cutaneous T-cell lymphoma (CTCL). In a phase 2 trial, 24 patients received pembrolizumab (2 mg/kg every 3 weeks) for up to 2 years. With a median follow-up time of 40 weeks, the ORR was 38% with 1 CR and 8 PRs. Six of the responding patients had greater than 90% improvement in cutaneous disease. Responses were durable with 89% ongoing at a median duration of 32 weeks (4-46). The one-year PFS was 69%. Treatment was well tolerated, except 25% of patients experienced skin flares upon treatment initiation; all of whom had Sézary syndrome. Interestingly, in patients who experienced a skin flare, increases in IFN-γ, IL-12p40, IL-15, LIF, G-CSF, and CCL4 occurred following treatment[104].

As previously mentioned, NKTCLs appear to facilitate immune escape via upregulation of the PD-1/PD-L1 axis[88]. A recent retrospective analysis of 7 patients with R/R NKTCLs

who had failed asparaginase containing chemotherapy regimens were treated with salvage pembrolizumab. This resulted in objective responses for each patient, with 5 patients achieving durable CRs. PD-L1 status was available in 5 of the patients, 4 of whom had high PD-L1 expression and 1 with weak expression by IHC. Of the patients with high PD-L1 expression, 3 achieved a CR[105]. Similar results have been observed following treatment with nivolumab[106].

Nivolumab has also been studied in patients with T-cell NHL as part of the Checkmate-039 trial[100]. In this phase 1, open-label, dose-escalation trial, 23/81 patients had T-cell NHL [13 patients with mycosis fungoides (MF), 5 with peripheral T-cell lymphoma (PTCL), 2 with Sézary syndrome CTCL, and 3 with other non-CTCL]. Twenty-two percent of patients with T-cell NHL suffered grade 3/4 AEs, with the most common being pneumonitis. For patients with MF, the ORR was 15%, with a CRR of 0%. Median PFS was 10 weeks (95% CI; 7–35). For patients with PTCL, the ORR was 40%, with a CRR of 0%. Median PFS was 14 weeks (95% CI; 3-NR). For patients with Sézary syndrome CTCL and other non-CTCL, the ORR was 0%[100].

Currently, there are several trials investigating the role of checkpoint inhibitors in combination with approved agents for T-cell lymphoma. This includes pembrolizumab with romidepsin (NCT03278782), pembrolizumab with decitabine and pralatrexate (NCT03240211), durvalumab with lenalidomide (NCT03011814), or checkpoint inhibitors with radiotherapy (NCT03385226 & NCT03235869).

The introduction of immune checkpoint inhibitors over the past decade has revolutionized the treatment of cancer. This has also been seen for the treatment of lymphoma. Future studies will need to focus on which lymphoma subtypes best respond to checkpoint inhibitors and the best indication for them. Outside of cHL, data for other subtypes of lymphomas is still small and further studies will need to be performed. Reliable biomarkers indicating which patients may respond to treatment in other subtypes of lymphoma outside of cHL need to be developed. Furthermore, when treating patients with aggressive lymphomas, historically responses are fast after the use of conventional chemo-immunotherapy. With immune checkpoint inhibitors, it may take weeks to months before a response is seen, and at that time a patient may be have worsening symptoms or be mislabeled as having progressive disease. Thus, for patients with aggressive lymphomas, future strategies that focus on combining immune checkpoint inhibitors with known or novel therapies may more effective. Also, the potential of combining checkpoint inhibitors in the setting of ASCT or Allo-SCT will also need to be evaluated, as they may be able to improve eradication of MRD in these settings.

Vaccines

One of the major advantages of treatment with immunotherapy *vs.* targeted therapies, is the ability to induce a durable adaptive immune response against the tumor[107]. While treatment with targeted therapies over time can lead to the development of resistant clones, yielding the therapy ineffective. B-cell lymphomas are clonal, forming from a single B-cell, with each cancer cell's B-cell receptor (BCR) expressing the same immunoglobulin heavy-chain variable region. This immunoglobulin idiotype (Id) is tumor specific and is a particularly attractive target for vaccine therapy[108]. The interaction between the tumor microenvironment and lymphoma cells in indolent B-cell lymphomas is attractive for vaccine therapy, as indolent lymphomas are particularly dependent on signaling by tumor-infiltrating immune cells for survival and growth. For example, follicular lymphomas have been found to be dependent on anti-apoptotic signaling from CD40+ dendritic cells (DCs)[109]. Thus, vaccination strategies that can augment signaling of tumor-infiltrating immune cells within the tumor microenvironment have the potential to provide durable responses. Moreover, after completing initial frontline therapy for indolent lymphomas, most patients will have a long enough remission that their immune system will have time to recover. It is at this point while burden of disease is low, and immune reconstitution has occurred, that vaccination strategies would be ideal.

Thus far most vaccine approaches for the treatment of lymphoma have been directed against Id antigens. Id peptides or whole Id determinants have been used to vaccinate patients as solely DNA or protein-based vaccines, or alternatively as DNA or proteins loaded into DC vaccines[110]. The difference between the two approaches, is that DNA or protein-based vaccines will illicit DC responses *in vivo* after vaccination, while DC loaded vaccines *ex vivo* allow for the generation of tumor antigen specific DCs, that activate the immune system upon injection *in vivo*[110].

DNA-based vaccines

DNA vaccines offer several advantages because multiple tumor antigens can be included into one vaccine, overall low cost to construct, and straight-forward production. For Id DNA-based vaccines, the immunoglobulin chains are clones and inserted into a plasmid vector for injection. The specific antigen is presented on local APCs, and DCs are recruited, helping generate an adaptive immune response. While initial

clinical trials with DNA-based vaccines demonstrated them to be safe, feasible, with modest anti-tumor immune responses, there was no clinical benefit attained[111]. Currently, approaches have focused on conjugating the Id sequence to immunostimulatory sequences to enhance DC chemotaxis and antigen presentation. This has included fusing it with the tetanus toxin, cytokine producing gene, chemokines, and viral proteins[112].

Protein-based vaccines

Initially, protein-based vaccines were challenging to make because they were patient specific, thus requiring a personalized vaccine product. However, advances in hybridoma technology, where the Id protein is generated by fusing lymphoma cells with mouse myeloma cells to create Id-producing hybridomas helped overcome these challenges. Alternative strategies have also included cloning tumor specific Id genes into cell lines that will subsequently produce the protein[108]. Since the Id protein is weakly immunogenic by itself, investigators have chemically coupled it with keyhole limpet hemocyanin (KLH) and co-administered it with granulocyte-macrophage colony-stimulating-factor (GM-CSF) to enhance immunogenicity. This strategy has been found to be successful in producing tumor-specific adaptive immune responses in both preclinical and early phase clinical trials[113]. These early promising results lead to three phase 3 randomized control trials of Id-KLH peptide-based vaccines in combination with GM-CSF for patients with FL after treatment with initial frontline chemo-immunotherapy.

Levy et al.[114] studied a recombinant Id peptide-based vaccine, *MyVax*, in 287 patients with advanced stage FL after receiving 8 cycles of CHOP. Patients achieving a PR or CR were randomized 2:1 to 7 months of *MyVax*, where the primary end of point of the study was to assess PFS. At a median follow-up of 58 months, median PFS was 19.1 months and 23.3 months (HR 0.98; 95% CI, 0.72–1.33) in the experimental *vs*. the control arms respectively. However, in patients with humoral immune responses observed (41%), the median PFS was significantly longer (40 months) (**Table 3**). Freedman et al.[115] studied a recombinant Id-KLH peptide-based vaccine, *mitumprotimut-T*, in 349 patients with either treatment-naive or relapsed/refractory disease achieving a complete response (CR), partial response (PR), or stable disease (SD) after receiving four weekly rituximab infusions. Patients were then randomized to either receive *mitumprotimut-T* + GM-CSF or placebo + GM-CSF until disease progression. The primary end point was TTP. The median TTP was 9 months for *mitumprotimut-T*/GM-CSF and 12.6 months for placebo/GM-CSF (HR = 1.384; P = 0.019). Lastly, Schuster et al.[116] studied a hybridoma derived Id-KLH peptide-based vaccine in 177 patients with advanced stage FL who achieved a CR after receiving frontline prednisone, doxorubicin, cyclophosphamide, and etoposide (PACE) chemotherapy.

Patients were randomized 2:1 to receive either vaccination with Id-KLH/GM-CSF or control (KLH/GM-CSF). The primary endpoint was disease free survival (DFS). At a median follow-up of 56.6 months, median DFS arm for vaccine was 44.2 months and 30.6 months for the control arm (HR, 0.62; 95% CI, 0.39 to 0.99; P = 0.047). Patients who were treated with IgM isotype vaccines compared to IgG isotypes had better outcomes (52.9 *vs*. 28.7 months; P = 0.001). Of the three trials, only Schuster et al.[116] found a survival benefit with vaccination. This might be because patients who were vaccinated in this trial were in a CR prior to vaccination. Thus, significant tumor burden may interfere with developing an adequate adaptive immune response after vaccination, and thus treatment strategies to employ Id-KLH peptide-based vaccines to treat MRD instead of active disease may have better success. Furthermore, using hybridomas and IgM isotypes to construct a peptide-based vaccine may also be important, as this may produce more immunogenic vaccines. Preclinical data has supported this approach as Id IgM isotypes are more immunogenic, while class switching to IgG can yield tolerance[116].

DC-based vaccines

To improve protein-based vaccines, researchers began investigating methods to load antigen presenting DCs *ex vivo* with TAA's, then stimulate them, and subsequently inoculate hosts. DCs are isolated from peripheral blood monocytes and differentiated by a combination of cytokines. The source of TAAs has varied, and has included tumor derived peptides, proteins, whole tumor lysates, or apoptotic bodies[110]. Initial studies using Id protein-based and tumor lysate pulsed dendritic cell vaccination were able to illicit significant T- and B-cell adaptive immune responses with durable clinical benefit for patients with B- and T-cell NHL[117-119]. Di Nicola et al.[119] treated 18 patients with relapsed indolent B-cell NHL with a DC loaded killed autologous tumor cell vaccine. The ORR was 33%, with 3 CRs, and only 4 patients with disease progression. Interestingly, specific humoral responses against lymphoma antigens were detected in responding patients,

Table 3 Summary of key vaccine therapy clinical trials for treatment of lymphoma

Study	Lymphoma subtype	Vaccine type	Induction therapy	Patients (*n*)	Immune response	Efficacy
Levy et al.[114]	Untreated FL	Protein-based; Id-KLH + GM-CSF *vs*. KLH + GM-CSF	CVP	287	Anti-Id humoral responses in 41% of treated patients.	Median PFS 19.1 months (experimental) *vs*. 23.3 months (control)
Freedman et al.[115]	Untreated FL	Protein-based; Id-KLH + GM-CSF *vs*. placebo + GM-CSF	Rituximab	349	N/A	Median TTP 9 months (experimental) *vs*. 12.6 months (control) (HR = 1.384; P = 0.019)
Schuster et al.[116]	Untreated FL	Protein-based; Id-KLH + GM-CSF *vs*. KLH + GM-CSF	PACE	177	IgM isotype vaccines compared to IgG isotypes improves survival (52.9 *vs*.28.7 months, P = 0.001)	Median DFS 44.2 months (experimental), *vs*. 30.6 months (control) (HR, 0.62; P = 0.047)
Di NiCola et al.[119]	R/R indolent B-cell NHL	DC loaded killed autologous tumor cell vaccine	N/A	18	Humoral responses against lymphoma antigens. Decrease in regulatory T-cells and increase in cytotoxic NK cells	ORR 33%, with 3 CRs
Brody et al.[126]	R/R indolent B-cell NHL	*In situ* vaccination with CpG DNA + XRT	N/A	15	Vaccination resulted in the development of tumor-reactive memory CD8+ T-cells	ORR 27%, with 1 CR
Kim et al.[127]	R/R CTCL	*In situ* vaccination with CpG DNA + XRT	N/A	15	Immunized sites appeared to demonstrate a reduction in infiltration of regulatory T-cells	5 clinical responses noted

with an overall decrease in regulatory T-cells and increase in cytotoxic NK cells. Approaches to improve upon DC-based vaccines include fusion of DCs with tumor cells, loading DCs with tumor mRNA, as well as enhanced antigen presenting tumor cell vaccination[120-122].

In situ vaccination

While DC loaded *ex vivo* vaccines appear to be more immunogenic with promising response rates, they are still incumbered by the fact that they require cell processing. Toll-like-receptor (TLR) agonists are known to stimulate innate immunity, enhancing antigen presentation by DCs, that can subsequently lead to the activation of the adaptive immune system[123]. CpG oligodeoxynucleotides (CpG DNA) is a TLR-9 agonist, that has been demonstrated to have robust anti-lymphoma activity in preclinical models both in combination with DC tumor-antigen loaded vaccines and in combination with chemotherapy with injected intra-tumorally. (*in situ* vaccination)[124,125]. *In situ* vaccination has the advantage that it provides tumor antigens to antigen-presenting cells, *in vivo*, allowing APCs to subsequently present to endogenous T-cells. Furthermore, it does not require patient specific cell processing, which can be costly and time-intensive. Brody et al.[126] treated 15 patients with relapsed indolent B-cell NHL with local radiation followed by a single intra-tumoral injection of CpG DNA. Overall, treatment was well tolerated. The ORR was 27%, with one CR. Correlative analysis demonstrated that vaccination resulted in the development of tumor-reactive memory $CD8^+$ T-cells. Similarly, Kim et al.[127] used the same approach to study *in situ* vaccination in 15 patients with relapsed MF. Five clinical responses were noted, with responses both at the primary and at distant sites. Interestingly, immunized sites appeared to demonstrate a reduction in infiltration of regulatory T-cells. More recently, *in situ* vaccination strategies using The Stimulator of Interferon Gene (STING) agonists, in combination with ibrutinib, and in combination with inhibitors of PD-1 and OXO-40 have been found to have significant anti-lymphoma activity in preclinical models[128-131].

In situ vaccination strategies have also been used for the treatment of MRD during transplantation. Chu et al.[132] studied the use of immunotransplant in patients with MCL. In this approach prior to treatment, patient's lymphoma cells are collected, a patient-specific vaccine is created by incubating fresh tumor cells with CpG DNA, and then cryopreserved. Patients then receive standard chemoimmunotherapy, and those that at least achieve a PR subsequently receive 3 sequential subcutaneous autologous tumor vaccinations mixed with CpG DNA. Vaccine primed T-cells are then harvested. After ASCT, patients receive primed T-cells and a 4th vaccination, followed by a 5th vaccination at 3 months after ASCT. In the interim analysis of the initial phase 1/2 clinical trial, 24 patients had been treated, with a 1-year after ASCT freedom from MRD of 90.5%. The 3-year PFS and OS at interim analysis are 54.5% and 63.6%, respectively. Investigators found that higher expression of co-stimulatory molecules on patient's lymphoma cells after treatment with CpG DNA was associated with improved freedom from MRD (P =0.02).

The safety and feasibility of vaccine therapy for the treatment of lymphoma has been demonstrated over the past 1–2 decades. Research have thus far demonstrated indolent lymphomas as the ideal subtype, with a focus of improving eradication of MRD in patients with CRs. The optimal vaccination strategy has not yet been identified, although *in situ* vaccination strategies that do not require *ex vivo* cell processing are demonstrating promising results. Combining vaccine therapies with immune checkpoint inhibitors to enhance anti-tumor response is a promising approach. This has been successfully studied in preclinical models, and is now being explored in early phase clinic trials (NCT 03121677)[108]. Furthermore, enhancing immunogenicity of vaccines by either targeting tumor-draining lymph nodes, or using nano-particle vaccine delivery systems is also currently being investigated[133].

Conclusions

Currently, the treatment for patients with lymphoma is undergoing a revolutionary shift. As more immunotherapeutic approaches become available, the use and need for conventional chemotherapy will continue to decline. The introduction of CD19-targeted CAR T-cell therapies, bispecific antibodies, and immune checkpoint inhibitors for R/R lymphomas have improved outcomes for chemotherapy refractory patients. However, even with treatment with CD19 CAR T-cells, only about half of patients will develop a CR. In contrast to treatment with chemotherapy however, patients who have PR or SD with immunotherapy can have meaningful and durable clinical benefit. Future studies will need to focus on novel targets, as well as combining current immunotherapeutic approaches to optimize treatment for patients with lymphoma. How to sequence treatment with the various immunotherapies will also need to be elucidated. Lastly, a focus on genetic and molecular biomarkers of a patient's lymphoma will likely help guide future clinical trials and treatment choices.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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