Review Article

Immunotherapy in non-Hodgkin lymphoma

Caron A. Jacobson, Philippe Armand

Dana-Farber Cancer Institute, Boston, MA, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Caron A. Jacobson, MD, MMSc. Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA.
Email: caron_jacobson@dfci.harvard.edu.

Abstract: The concept of co-opting an immune response to treat cancer has existed for centuries. Modern advances in our understanding of how the immune system is regulated, how a tumor evolves to evade an immune response, and how the immune system can be manipulated, both pharmacologically as well as genetically, have moved this concept from an ideal to reality, sparking a revolution in cancer therapeutics and the field of immuno-oncology. This review will focus both on cellular therapeutics, and specifically chimeric antigen receptor (CAR) T-cells, as well as immune checkpoint inhibition, in non-Hodgkin lymphoma (NHL). The former has had remarkable efficacy in a large number of patients, whereas the benefit of the latter has been restricted to specific histologies. As we learn more about the tumor microenvironment for each of the NHL histologies, mechanisms of resistance, and predictors of response, we will undoubtedly identify new combinations, or new ways to manipulate the immune system, to improve outcomes in these diseases.

Keywords: Immunotherapy; non-Hodgkin lymphoma (NHL); chimeric antigen receptor T-cell (CAR T-cell); checkpoint blockade

Received: 13 September 2018; Accepted: 28 November 2018; Published: 21 December 2018.
doi: 10.21037/aol.2018.12.01
View this article at: http://dx.doi.org/10.21037/aol.2018.12.01

Introduction

Cancer immunotherapy has been a focus of research and investigation since the recognition of T-cells as integral to the immune response in the mid-twentieth century (1). Allogeneic stem cell transplantation represents a powerful yet non-specific form of immunotherapy. Its curative potential in most subtypes of advanced non-Hodgkin lymphoma (NHL) strongly supports a role for immunotherapy in these diseases. However, strategies to induce a host anti-tumor immune response without the complexity and toxicity of allogeneic adoptive immunotherapy have been very challenging to develop. The first therapeutic advance in pharmaceutical immune-oncology was the use of recombinant IL-2 in renal cell carcinoma and melanoma, leading to the Food and Drug Administration (FDA) approval of high dose recombinant IL-2 for these diseases in 1992 and 1998, respectively (2,3). Since that time, the ability to generate monoclonal antibodies against tumor antigens and to use tumor antigens in order to educate the immune system through tumor vaccines moved the field closer to a tumor-specific immune response (4,5). Similarly, the discovery of, and ability to grow and expand, tumor infiltrating lymphocytes (TILs) for reinfusion into melanoma patients laid the groundwork for cellular immunotherapy (6,7). Further genetic engineering of autologous T-cells with either engineered T-cell receptors (eTCRs) or chimeric antigen receptors (CARs) directed against tumor antigens has expanded the field of adoptive immunotherapy and the breadth of target diseases (8-10). Finally, the discovery of immune checkpoint molecules like cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) and the elucidation of their role in tumor immune evasion has led to the development of inhibitory therapeutic monoclonal antibodies for the treatment of cancer patients

which have revolutionized oncology (11-15). Since the FDA approval of high dose IL-2 in the 1990s, the field has seen the approval of a tumor vaccine for prostate cancer (16), two CAR T-cell products targeting CD19 (17,18), and several immune checkpoint blockade inhibitors in a variety of tumors (13-15). Together, these advances have established immune-oncology as a fundamental paradigm in the treatment of tumors across the cancer spectrum. The impact on the treatment of patients with NHL has been variable and heterogeneous among immunotherapy modalities and tumor targets, which reflects the complex and heterogeneous biology of NHL. The most recent and promising avenues of treatment are CAR-T-cells and immune checkpoint blockade. This review will explore their efficacy and limitations in NHL.

CAR T-cells in NHL

The discovery and clinical application of TILs really laid the groundwork for the revolution in engineered cell therapies, which is poised to soon change treatment paradigms in NHL. Following the initial promising results in melanoma, research shifted towards the genetic engineering of autologous T-cells with gene constructs for eTCRs or CARs directed toward tumor antigens. T-cells have been engineered to target dozens of tumor antigens and have been tested in clinical trials in an equally broad number of tumor types. To date, their greatest success has been with anti-CD19 directed CAR T-cells in B-cell acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL) and other B-cell NHLs.

Anti-CD19 CAR T-cell efficacy

In 2010, investigators at the National Cancer Institute (NCI) reported the results of the first NHL patient to have been treated with anti-CD19 directed CAR T-cells (19). The CAR construct contained a CD28 costimulatory molecule and would later be developed as axi-cel. This patient with heavily pre-treated follicular lymphoma had a partial response (PR) with subsequent progression at 32 weeks, but CD19+ B-cells were absent from the blood or bone marrow at 36 weeks and CAR T-cells were detected in the blood through 27 weeks following infusion. This provided a proof-of-principle that CAR T-cells could persist and launch a successful immune attack on target cells. Five years later, the same group reported their experience with this construct in 15 patients with B-cell NHL [including DLBCL and primary mediastinal B-cell lymphoma (PMBL)] and chronic lymphocytic leukemia (CLL) (20). The overall response rate (ORR) was 92%. Among seven DLBCL patients, the CR rate was 57% and the ORR was 86%. The ORR in indolent lymphoma and CLL was 100%. Many responses were durable through the 22-month follow-up.

The early success of axi-cel in B-cell NHL, and in DLBCL and PMBL in particular, led to the pivotal phase 2 ZUMA-1 study in patients with refractory high-grade B-cell lymphoma (HGBL), DLBCL, PMBL, and transformed follicular lymphoma (tFL) (18). This multicenter study treated 101 out of 111 enrolled chemotherapy refractory patients with axi-cel. No bridging therapy was allowed and the average manufacturing time from leukapheresis to the delivery of the product was 17 days. There was only one manufacturing failure; the other 9 patients did not receive their cells due to adverse events, disease progression or because they had unmeasurable disease prior to lymphodepleting chemotherapy. Among the treated patients, ORR was 82% (82% in DLBCL/HGBL; 83% in PMBL/tFL). Complete responses were observed in 54% of patients (49% in DLBCL/HGBL; 71% in PMBL/tFL). There was no clear association between response and any baseline patient or disease characteristic, including CD19 positivity. Response was associated higher peak levels of CAR T-cells. As in the early phase study, responses were durable, with 70% of complete responses (CRs) (42% of treated patients overall) maintained after a median of 15.4 months. These results compared favorably with those of a historical cohort of similar patients assembled for purpose of this comparison, with CR rates of 54% (with axi-cel) versus 7% and median overall survival (OS) not reached at >15 months versus a median OS of 6.3 months (21). This study led to the FDA approval of axi-cel for the treatment of relapsed/refractory DLBCL, HGBL, PMBL and tFL following 2+ prior lines of therapy in October 2017.

A second anti-CD19 CAR T-cell construct, tisagenlecleucel (t-cel) was FDA approved for the treatment of relapsed/refractory DLBCL, tFL, and HGBL after two prior lines of systemic therapy in April 2018 based on the results of the pivotal JULIET study by Novartis. This construct contains a 4-1BB rather than a CD28 costimulatory domain, which differentiates it from axi-cel. In preclinical models, CD28 constructs had a more rapid and higher peak CAR T-cell expansion than 4-1BB CAR T-cells (22). T-cel was tested in a pilot study in 28 patients with DLBCL (n=14) or FL (n=14) (23). In this

study, bridging chemotherapy was allowed and administered to 10/28 patients. The median time from apheresis to infusion was 39 days. The ORR in DLBCL was 50%, with 43% CRs. In FL, the ORR was 79%, with 71% CRs. At a median follow-up of 28.6 months, 86% of DLBCL and 89% of FL responders (43% and 70% of treated DLBCL and FL patients, respectively) remained in response. Although the sample size was small, response in DLBCL appeared to be independent of cell of origin, high-risk cytogenetics, and disease burden. Among 10 patients with DLBCL and available pre-treatment biopsies, responding patients had lower levels of PD-L1, PD-1, LAG3, and TIM3 in the tumor and tumor microenvironment. CAR T-cells were detectable in almost all patients in response between 6 and 24 months. Only 2 patients in response lost detectability of CAR T-cells early after their infusion. Similarly, lack of B-cell depletion was associated with early disease progression in 2 patients; all patients in CR had B-cell depletion, and in half this was ongoing at 6.7 months.

The follow-up pivotal, multicenter JULIET study screened 160 patients to treat 106; 49 patients did not receive their cells due to declining health or disease progression (n=38) or due to an inability to manufacture cells (n=11). Patients were eligible for this study if they had relapsed or refractory DLBCL/HGBL or tFL following 2 or more prior lines of therapy. Bridging chemotherapy after apheresis was allowed and given to 90% of patients. The FDA reviewed data for 68/92 patients dosed in the US with at least 3-month follow-up (Kymriah package insert). Some patients not included either did not have lymphoma (n=1), or had achieved a CR following bridging chemotherapy (n=8). Among these 68 patients, the ORR was 50%, with a CR rate of 32%. With a median follow-up of approximately 6 months, approximately 30% of patients remain in CR and 7% of patients remain in PR. Durable responses were associated with T-cel persistence, lasting up to 378 days after infusion in some patients.

A third anti-CD19 CAR T-cell product, lisocabtagene maraleucel (liso-cel) is being developed by Juno Therapeutics for the treatment of relapsed/refractory DLBCL/HGBL, PMBL and tFL following 2 or more prior lines of therapy. Like T-cel, this construct has a 4-1BB costimulatory domain. One distinguishing characteristic of liso-cel is that it is engineered to have a defined composition of CD4+ and CD8+ CAR T-cells. The TRANSCEND-NHL study of liso-cel in B-cell NHL initially enrolled a more heterogeneous group of B-cell NHL patients, testing different doses and dosing schedules. The CORE cohort was later defined to include only patients with DLBCL/HGBL and tFL as part of the pivotal study, and included 73 patients (24). Of patients apheresed, 13 did not receive treatment due to progressive disease and/or death, 2 patients hadn't received product due to an inability to manufacture cells, and 5 patients had withdrawn consent. Twelve patients are not included in the analyses as they received a cellular product that did not meet product specifications. Within the CORE cohort, the ORR was 80%, with a CR rate of 59%. Approximately 80% of CRs (41% of treated patients) remained in response at 6 months. Response was independent of adverse prognostic factors for these diseases, as was seen in the ZUMA-1 and JULIET studies (24).

The success of these 3 CAR T products in relapsed/refractory DLBCL/HGBL, PMBL and tFL has provided the impetus for many ongoing and planned studies in different settings and in different NHL subtypes. For example, axi-cel is currently being evaluated in indolent B-cell NHL (ZUMA-5, NCT03105336) and mantle cell lymphoma (ZUMA-2, NCT02601313). It is also being tested in a randomized trial against standard of care therapy [salvage chemotherapy/autologous stem cell transplant (ASCT)] in the second-line setting for patients with primary refractory, or early relapsing (<12 months) DLBCL, HGBL, and tFL (ZUMA-7, NCT03391466). Similar trials for t-cel and liso-cel are in the pipeline.

Anti-CD19 CAR T-cell toxicity

While anti-CD19 CAR T-cell therapy has had remarkable efficacy and has established a new and effective standard of care for relapsed/refractory aggressive B-NHL, it is associated with unique and important toxicities, most notably cytokine release syndrome (CRS) and neurotoxicity. The incidence of these toxicities varies with target antigen and target disease, and likely with the different constructs. For example, both CRS and neurotoxicity occur at higher frequency in B-ALL than B-NHL. There is also a higher incidence of neurotoxicity with anti-CD19 directed CAR T-cells than those that target other antigens, like BCMA. High tumor burden and pretreatment inflammatory markers may also associate with higher rates and grade of toxicity. Whether there is more high-grade CRS or neurotoxicity with CD28, as compared with 4-1BB, CAR T-cells constructs is not yet clear. Because of theoretical differences in kinetics of CAR T-cell expansion, it has been hypothesized that rates of high-grade CRS and/or neurotoxicity may be increased following treatment with

CD28 CAR T-cells. While there have been differences reported across the studies to support this hypothesis, caution may be warranted in comparing across studies. First, the patient numbers are small. Second, the patient populations treated on these studies are different, as was their management prior to and after CAR-T infusion. Patients on the ZUMA-1 study had refractory disease, whereas patients on the JULIET and TRANSCEND studies had either relapsed or refractory disease, which could mean they had decreased tumor bulk or were less sick as their disease had not been growing through their last line of therapy. Bridging therapy was allowed on JULIET and TRANSCEND, and while it is not expected that these patients would have a durable response to such chemotherapy, a transient response was possible, yielding an improved disease burden at the time of their CAR T-cell infusion. In support of this is the fact that eight patients on the JULIET study had a complete response to bridging therapy prior to CAR T-cell infusion.

CRS

The rapid expansion and activation of T-cells upon reinfusion into a patient with an active CD19+ B-cell malignancy is associated with release of pro-inflammatory cytokines like IL-6, IL-15, and INF-g, among others. The result is a clinical syndrome, CRS, of high fevers, fatigue, and malaise that can progress to cause hypotension, capillary leak, respiratory distress, and end-organ dysfunction. The timing, severity, and duration of CRS vary between different anti-CD19 CAR T-cell products, and by baseline patient and disease characteristics, but it typically occurs within 1–5 days of CAR T-cell infusion and lasts 5–8 days, corresponding with CAR T-cell expansion and peak CAR T-cell levels. It has been theorized that the CD28 CAR T-cell constructs may be associated with earlier and more pronounced CRS due to a more rapid CAR T-cell expansion.

The ZUMA-1 study used the Lee criteria (25) for CRS grading, and on this study 13% of patients experienced grade 3 or higher CRS (18). Any grade CRS occurred in 93% of patients. The median time to onset of CRS was 2 days, and the median duration of CRS was 8 days. There were two cases of fatal CRS, one due to hemophagocytic lymphohistiocytosis (HLH) and one due to cardiac arrest, while all other CRS events were fully reversible. At the outset of this study, little was known about the effect that drugs like tocilizumab and/or corticosteroids would have on the activity and efficacy of CAR T-cells and so they were used more sparingly. With data showing that they did not impact efficacy, they were used earlier as the study progressed and rates of grade 3 or higher CRS improved. In all, 43% and 27% of patients received tocilizumab and glucocorticoids, respectively.

The JULIET study used a CRS grading system developed at the University of Pennsylvania (26). In this scale, patients with grade 3 CRS would largely have had grade 2 CRS by Lee Grading. The incidence of grade 3 or higher CRS was 23%, but only 6% required vasopressor support, and the incidence of any grade CRS was 74% (Kymriah package insert). These results were similar to those observed on the single center experience with T-cel in B-cell NHL (23). The median time to CRS was 3 days, and the median duration was 8 days. Tocilizumab and/or steroids were administered to 21% of patients overall. Just over 25% of patients on the JULIET study received CAR T-cells as an outpatient and approximately 75% could remain outpatient for 3 or more days before developing CRS.

Finally, on the TRANSCEND study, the rates of any grade and grade 3 or higher CRS (Lee grading) were quite low, with only 37% of patients in the CORE cohort experiencing CRS of any grade (24). Only 3% of CORE patients had grade 3+ CRS. In the FULL cohort, the median time to onset of CRS was 5 days, with 7% of patients receiving tocilizumab and 10% receiving corticosteroids. Like with the JULIET study, the delay in onset of CRS allows for the potential of outpatient dosing of liso-cel, which is currently being explored.

Neurotoxicity

CAR-T induced neurotoxicity can manifest with a variety of clinical symptoms including confusion, aphasia, tremors, seizures, obtundation and coma. The pathophysiology of this syndrome is less well understood than that of CRS. Nonetheless, recent animal and human studies have described the importance of endothelial injury and increased blood-brain barrier (BBB) permeability, as well as the increase in levels of proinflammatory cytokines and CAR-T-cells in the cerebrospinal fluid (CSF) (27-31). One study in patients treated with anti-CD19 CAR-T demonstrated an association between high-grade neurotoxicity and early onset CRS, as well as with younger age, B-ALL diagnosis, tumor burden, and earlier and higher peak CAR T-cell expansion (29). High-grade neurotoxicity was associated with disseminated intravascular coagulation (DIC), higher angiopoietin (ANG) 2 to ANG1 ratio, and a low ADAMTS13 to vWF ratio consistent with an acquired

thrombotic microangiopathy (28,29). Consistent with other studies, high-grade neurotoxicity was associated with increased numbers of CAR T-cells as well as inflammatory cytokines in the CSF. Together these observations suggest a model by which CAR T-cell-induced inflammation can elicit endothelial activation as well as a brain pericyte stress response leading to increased permeability of the BBB and subsequent influx of proinflammatory cytokines and T-cells into the CSF. Fortunately, except in cases of fatal cerebral edema, which is rare, all neurotoxicity observed on the B-cell NHL studies has been completely reversible.

On ZUMA-1, the incidence of neurotoxicity of any grade was 64%, with 28% of patients experiencing grade 3+ neurotoxicity (18). Neurotoxicity generally occurred later than CRS, with a median time to onset of 5 days, and median resolution on day 17 following infusion. Again, severe neurologic toxicity on this study was associated with higher peak levels of IL-2, GM-CSF, and ferritin. On JULIET the incidence of neurologic toxicity was 58%, with 21% of patients experiencing grade 3 or higher neurotoxicity (Kymriah label). These numbers are higher than those seen on the single center experience with T-cel in B-cell NHL, where 39% of patients had neurotoxicity of any grade, and 11% of patients had grade 3 or higher neurotoxicity (23). One patient with FL on this study had grade 5 neurologic toxicity; at autopsy the brain exhibited diffuse gliosis with severe, widespread neuronal loss and white matter degeneration and a macrophage/CD8 T-cell infiltrate. On TRANSCEND, the incidence of neurotoxicity in the CORE cohort was 25%, with 15% experiencing grade 3 or higher neurotoxicity (24). There were no grade 5 neurologic events. The median time to onset of neurotoxicity was 10 days.

Anti-CD19 CAR T-cell resistance

There are two main mechanisms of CAR T-cell resistance that to date have been the focus of investigation, although there will likely be several more. The first is loss of target antigen, and the second is T-cell exhaustion and/or inhibition. Loss of CD19 has been described following anti-CD19 CAR T-cell therapy in both B-ALL and B-NHL. In B-ALL, 10–30% of patients will relapse with CD19 negative disease. Genetic analysis of two of these relapses demonstrated loss of one copy of CD19 and alternative splicing of the other, resulting in loss of exon 2, which had acquired frameshift or missense mutations that would have otherwise led to loss of expression of the second copy of CD19 and likely cell death (32). This truncated CD19 is not detected by CD19 immunostains or antibodies, fails to trigger CAR T-cell killing, and partially rescues the cancer cell from the effects of CD19 loss. Strategies in development to address antigen loss include the development of multivalent CAR T-cells that target more than one tumor antigen (33).

T-cell exhaustion is an alternative mechanism of CAR T-cell resistance that may be relevant across many tumor types. Primary resistance to adoptive immune effector cell transfer can occur in tumors that have an inhibitory tumor microenvironment, or that upregulate ligands for T-cell inhibitory receptors. In addition, upon antigen stimulation T-cells upregulate PD-1 and CTLA-4 on their surface while upon immune attack, tumor cells increase expression of ligands for those receptors. The result is an acquired form of resistance with T-cell exhaustion and immune escape. In mouse models of mesothelioma, PD-1 antibody therapy restored the function of anti-mesothelin directed CAR T-cells (34). There are case reports of the successful use of anti-PD-1 antibodies to patients having progressed following anti-CD19 CAR T-cell therapy in lymphoma; these clinical responses were associated with a rise in CAR T-cell numbers as well as an increase in pro-inflammatory cytokines within 24 hours of anti-PD-1 antibody therapy, and recrudescence of CAR T-cell related toxicities (35). There is now a study of pembrolizumab for the treatment of relapsed or refractory lymphoma following anti-CD19 directed CAR T-cell therapy (NCT02650999), as well as a phase 1/2 study of the PD-L1 antibody atezolizumab with axi-cel for refractory DLBCL (ZUMA-6, NCT02926833). Other strategies to overcome inhibition of CAR T-cells involve further genetic modification of CAR T-cells such that the genes for PD-1 and other inhibitory receptors are knocked out using gene-editing technologies. Alternatively, CAR T-cells are being engineered into "armored CARs", which have an inducible or constitutively active proinflammatory cytokine gene construct (e.g., IL-12) to improve CAR T-cell activation or persistence.

Finally, the exact composition of the infused CAR T-cell products is variable, even in liso-cel where the CD4:CD8 ratio is controlled. In addition to selecting for certain T-cell subsets, prior therapies may affect both the health of T-cells collected and the proportion of T-cell subtypes at leukapheresis. Drugs like ibrutinib have immunomodulatory effects that may improve CAR T-cell activity through its effect on T-cell subsets. The immunophenotype of effector CAR T-cells may be important, as response in CLL has

been associated with a higher proportion of memory-like CD8 T-cells with an IL6/STAT3 like gene signature, whereas resistance was associated with gene signatures associated with differentiation, glycolysis, exhaustion and apoptosis (36). Exploring new targets, new combinations, and new and additional ways of genetically engineering CAR T-cells are the major movements in the field to both improve outcomes in established diseases and to expand the indication for these therapies for new diseases.

Immune checkpoint blockade in B-cell NHL

As discussed above, targeting T-cell checkpoint or co-stimulatory pathways may emerge as an important platform to overcome resistance to CAR T-cell therapy. Its efficacy as a primary treatment strategy for relapsed/refractory B-cell NHL, though, has not been uniformly promising. The more common B-cell and T-cell NHLs largely lack significant overexpression of the PD-1 ligands PD-L1 and PD-L2, and perhaps as a consequence the efficacy of checkpoint inhibition in these diseases has been disappointing. However, certain subtypes of NHL with more frequent perturbations of PD-1 ligands may be more sensitive to PD-1 inhibition.

Immunologic features of the tumor and its microenvironment in NHL

Common subtypes of B-cell NHL, including DLBCL and FL, rarely (<10%) overexpress PD-L1 or PD-L2. Despite this, levels of PD-L1 and PD-L2 expression in these diseases do correlate with a worse outcome with chemoimmunotherapy (37). While the tumor cells themselves may not overexpress PD-L1 and PD-L2, the immunophenotype of the tumor microenvironment in these diseases may lead to tumor immune evasion. There is evidence that immune escape may play a role in DLBCL progression, given the incidence of mutations in the genes for β2-microglobulin (29%) and CD58 (21%) in this disease in addition to aberrations in HLA-1 and CD58 expression in the absence of genetic mutations; this may prevent recognition by, and activation of, CD8+ T-cells and NK cells, respectively (38). The tumor cell in DLBCL may also express chemokines and cytokines that attract and retain M2 macrophages and regulatory and exhausted T-cells within the microenvironment; pre-rituximab, an increased in intratumoral CD68+ macrophages was associated with inferior OS in this disease (39,40). Immune evasion therefore likely represents an important survival mechanism, but may not depend principally on engagement of the PD-1 pathway.

In FL, GEP identified two signatures associated with prognosis in the pre-rituximab era, which correlated with gene expression by tumor infiltrating immune cells (41). A profile including predominantly T-cell markers (immune-response 1) was more favorable, whereas a GEP including genes expressed by macrophages and dendritic cells (immune-response 2) was associated with worse outcomes. The use of rituximab, however, has paradoxically made the immune-response 2 signature a favorable prognostic marker (42). There are other reasons to suspect that FL can be targeted by immunotherapy. FL cells alter the gene expression of CD4+ and CD8+ TILs, resulting in impaired lymphocyte function and motility (43). Further interaction between FL cells and the microenvironment are being elucidated, such as the interactions between FL and follicular helper T (T_{FH}) cells and their effect on macrophage polarization and lymphoid differentiation (44,45), or the presence of distinct populations of CD4+ TILs differentiated by their level of PD1 and TIM-3 expression (46-48). A high proportion of PD-1+TIM3+ T-cells, representing exhausted T-cells, outside of the lymph node follicle has been associated with a poor prognosis, and inhibition of TIM3 by anti-TIM3 antibodies can restore function of these T-cells (47). Reports of the prognostic value of PD-1 expression on TILs in FL have been conflicting, however, and it may be that the impact on outcome is T-cell subset dependent (49,50). Altogether, these studies highlight the richness complexity of FL's interaction with the immune system, and hold the tantalizing promise of therapeutic success by disabling key mechanisms of immune escape.

While the above support a role for immune evasion in the pathobiology of DLBCL and FL, they do not specifically support the use of PD-1 blockade. In contrast, a number of NHL histologies have specific biological characteristics that suggest a potential dependence on the PD-1 pathway and vulnerability to PD-1 blockade. The model for this is classical Hodgkin lymphoma (HL), which harbors near-universal abnormalities at 9p24.1, resulting in amplification and overexpression of PD-L1 and PD-L2, as well as JAK2 (51). Gene expression profiling (GEP) highlights the relatedness of this disease to PMBL. Indeed, PMBL frequently overexpresses PD-L1 and PD-L2 as a result of genetic amplification or translocation events involving the PD-1 ligands (52,53). Gray zone lymphoma (GZL) between

HL and PMBL is a disease with a distinct methylation profile from PMBL and HL, although it shares some biologic and pathologic similarities with these diseases. Unsurprisingly, it also has frequent alterations at 9p24.1 (54). A genomic analysis of primary central nervous system lymphoma (PCNSL) and primary testicular lymphoma (PTL) revealed genetic similarities between these diseases and PMBL (55). His analysis identified recurrent copy number gains at 9p24.1 and translocations involving *PD-L1* and *PD-L2* in these diseases. These diseases (PMBL, GZL, PCNSL, PTL) share a high frequency of 9p24 abnormalities, which may render them susceptible to PD-1 blockade. In addition, in a separate analysis EBV+ DLBCL tumors were shown to have frequent overexpression of PD-L1, although in this case induced directly by EBV-encoded proteins rather than 9p24 deregulation (56). T-cell/histiocyte-rich large cell lymphoma (TCHRLCL) was also found to overexpress PD-L1 in a majority of patients while nodular lymphocyte-predominant HL was found to have high PD-L1 expression in one study but not another (57,58). A small series of patients with Richter syndrome (RS) with a high response rate to PD-1 blockade sparked interest (59). Interestingly, these lymphomas frequently overexpress PD-1, not PD-L1 (80%) (60). Finally, several T-cell lymphomas and histiocytic tumors overexpress PD-L1, including ALK+ anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL), the virally-driven entities NK/T-cell lymphoma and adult T-cell leukemia/lymphoma, and follicular dendritic cell sarcoma (57). PD-L1 expression within tumor cells has been seen in up to 27% of patients with cutaneous T-cell lymphoma (CTCL) and 15% of patients with peripheral T-cell lymphoma (PTCL), but expression in the tumor microenvironment is much higher (73% and 39%, respectively) (61). Certain T-cell lymphoma subtypes, like cutaneous T-cell lymphomas, are associated with a high mutational burden, which has been associated with greater response to checkpoint blockade in other cancer subtypes (62).

Clinical experience of immune checkpoint blockade in NHL

DLBCL

As discussed above, DLBCL not otherwise specified (DLBCL NOS), which represents the most common lymphoma diagnosis worldwide, rarely overexpresses PD-L1 or PD-L2. Initially, the phase 1 results with nivolumab were encouraging with an ORR of 36%, and one durable response (63). Unfortunately, the as yet unpublished results of the CheckMate-139 phase 2 study of nivolumab in DLBCL NOS did not confirm the earlier results, with an ORR of 3% and 10% in patients who were ASCT ineligible or who had relapsed after ASCT, respectively. Median duration of response was 8.3 and 11.4 months in the 2 cohorts respectively and median duration of complete response has not yet been reached (clinicaltrials.gov). This suggests that remissions in DLBCL are rare, but may be durable when they do occur, and support the idea of testing this modality in specific subsets as discussed below.

The use of checkpoint inhibition in DLBCL may be more effective in combination. A phase 1 study tested the combination of PD-1 and CTLA-4 blockade, with preliminarily no indication of improvement in ORR (64). Despite this, other combinations are currently being explored. These include combinations of PD-1 blockade with agonist antibodies against 4-1BB (utomilumab; NCT02951156) or CD27 (varlilumab; NCT03038672), as well as with other immunomodulatory agents like lenalidomide or ibrutinib. Through correlative and biomarker-driven science on these studies, taking advantage of technical improvements in immunologic profiling both in the tumor and in the blood, the immunologic synapse of this disease may soon be better understood, informing rational and more effective combinations and targets.

Follicular lymphoma

Somewhat more is known about the interface between FL and the immune system, and there is evidence that this disease is sensitive to immunologic surveillance as demonstrated by the efficacy of allogeneic stem cell transplant and reports of spontaneous remissions in this disease. A few FL patients were treated on the early phase studies of immunotherapy agents like pidilizumab and ipilimumab and responses were seen (65,66). These patients were included in a phase 1 study of nivolumab, with ORR of 40% and a CR rate of 10% (63). Unfortunately, as in DLBCL these early promising results were not replicated in phase 2. In unpublished results from the CheckMate-140 trial of nivolumab, the ORR was only 4%, with one patient out of 92 achieving a complete response. Among the few responding patients, responses were durable with a median duration of response of 10.4 months, but the median progression-free survival (PFS) was only 2.2 months (clinicaltrials.gov). Combination of PD-1 blocking agents with anti-CD20 antibodies like rituximab has yielded more encouraging results, although they were tested in patients

with rituximab-sensitive disease, where the expected benefit of CD20 directed therapy will be higher. Clinical trials of rituximab or obinutuzumab with pembrolizumab or atezolizumab, respectively, have yielded encouraging results with ORRs in the 57–67% range (67,68). Median duration of response to rituximab/pembrolizumab was 14.1 months, and median PFS was 11.4 months. With the R-pembrolizumab combination, the CR rate was 50%, which does suggest a possible synergistic effect of the combination. Furthermore, this study included blood and tumor biomarker analysis; there was no relationship between PD-L1 levels by immunohistochemistry in the tumor and response, but there was a relationship between a CD8 effector gene signature and the interferon-γ score in the blood and response. Rituximab in combination with immunotherapy targeting other T-cell receptors, including the 4-1BB agonist antibody utomilumab, has also been explored. This combination yielded responses in 27% of patients, including responses in one-third of patients with rituximab-refractory disease (69). Numerous combination studies are underway combining PD-1 or PD-L1 blocking agents with histone deacetylase inhibitors, lenalidomide, ibrutinib, chemotherapy, or other immunotherapy agents. As in the case of DLBCL, correlative science involving tumor and blood samples on these trials will inform a rational immunotherapy approach to the treatment of this innately immunosensitive tumor.

T-cell lymphomas

Twenty-three patients with T-cell lymphomas, including CTCL (n=13) and PTCL (n=5), were included on the phase 1 nivolumab trial; ORR was 15% in CTCL patients and 40% in PTCL (63). Two responding patients had responses that were ongoing at 24- and 50-week follow-up, and one patient had a response ongoing at 18 months. Further investigation of pembrolizumab in CTCL and Sezary syndrome resulted in ORR of 55% and 27%, respectively, with durable responses in responding patients and patients achieving disease stabilization (70). The 12-month PFS was 69%. These results are provocative, although given the tremendous biological heterogeneity of T-NHL, larger studies are needed to better understand the role of PD-1 blockade in these diseases. There are also several ongoing studies exploring combinations of PD-1 or PD-L1 with other agents active in T-cell lymphoma, including pralatrexate, romidepsin, azacitidine, and lenalidomide.

PD-L1/PD-L2 overexpressing lymphomas

The ability to selectively target specific lymphoma subtypes with PD-1 blockade based on their biology has already yielded several encouraging results. Based on the known recurrent alterations in *PD-L1* and *PD-L2* in PMBL, these patients were included in the phase 1 KEYNOTE-013 study of pembrolizumab in patients with hematologic malignancies. Amongst seventeen patients with PMBL, the ORR was 41%, with a CR rate of 12% (71). These responses were durable, with 6/7 responding patients remaining in response at a median follow-up of 11.3 months. These promising results, as well as the early experience of checkpoint inhibition in RS (ORR 44% in 9 patients), led to a phase 2 study of pembrolizumab in PMBL and RS, which treated 53 patients with PMBL (KEYNOTE-170, NCT02576990) (59,72). At last report the response rate in PMBL was 45%, with a CR rate of 11. The median duration of response had not been reached at ~10 months. This led to the FDA approval of pembrolizumab in PMBL after failure of 2+ lines of prior therapy. Results in Richter's transformation have not yet been reported. In one small case series, PD-1 blockade yielded complete responses in 3 of 3 patients with GZL (73). Based on the identification of recurrent alterations involving *PD-L1* and *PD-L2* in PCNSL and PTL, 5 patients with PCNSL (n=4) or secondary CNS lymphoma (n=1) were treated off-label with the anti-PD-1 antibody nivolumab (74). The ORR was 100%, with a CR rate of 80%. These responses were durable, ranging from 13+ to 17+ months. Based on these results, nivolumab is being investigated in relapsed/refractory PCNSL and PTL (CheckMate-647, NCT02857426). The EBV-driven NK/T-cell lymphoma also seems to be a good target for PD-1 blockade, with an ORR of 100% in a small study (75). An ongoing multicenter phase 2 study is currently testing pembrolizumab in biologically selected subtypes of lymphoma and hematologic malignancies including EBV+ lymphoma, T-cell/histiocyte rich DLBCL, plasmablastic lymphoma, AITL, and several histiocytic disorders (NCT03316573).

Targeting the innate immune system

Immune checkpoint blockade has mostly targeted PD-1 (and less commonly in NHL CTLA-4) to date, but advances in the understanding of how the innate immune system is regulated identified new potential immunotherapy targets in oncology. The "don't eat me" molecule CD47, which is overexpressed by a large variety of cancers including

DLBCL and FL, binds to a receptor on macrophages and prevents phagocytosis of the cancer cell. Hu5F9 is a first-in-class monoclonal antibody to CD47. It was tested in combination with rituximab in a phase 1 study in relapsed/refractory DLBCL and FL, 90% of which were rituximab-refractory, with promising results (76). ORRs were 40% and 71% in DLBCL and FL, respectively, with CR in up to 1/3 of DLBCL patients and 43% of FL patients. These responses to date have been durable, with 91% of patients remaining in response at a median follow-up of 6 months and one CR ongoing at 14+ months, but the follow-up overall has been short. The phase 2 study of this combination is ongoing (NCT02953509). Targeting the innate, rather than adaptive, immune system may represent an effective strategy in these diseases.

Conclusions

The field of cancer immunotherapy has grown by leaps and bounds since the early days of high dose IL-2 therapy and allogeneic stem cell transplantation. Through an improved understanding of how the immune system is regulated, and new techniques in genetic engineering, we can now target tumors effectively with both antigen-independent and antigen-specific therapies. The most promising immunotherapeutic innovation in NHL, and in B-cell NHL in particular, has been anti-CD19 directed CAR T-cell therapy, with durable responses seen in nearly 40% of patients with advanced aggressive B-cell NHL. This therapy is now being explored in other B-cell NHL subtypes, including indolent lymphomas and mantle cell lymphoma. Emerging information regarding mechanisms of resistance with this therapy has informed strategies to enhance immune activation of effector T-cells, either through their use in combination with immunomodulatory agents or through further genetic modification. While immune checkpoint blockade has been so far disappointing in all-comer trials of DLBCL and FL, the biologically predictable success of PD-1 blockade in HL has allowed similar biological insights to direct PD-1 blockade to apparently vulnerable NHL subtypes, most notably PMBL. Although numerous combination studies are currently underway with both checkpoint blockade and CAR T-cells, a better understanding of the immune synapses and immune microenvironment in each specific NHL subtype will undoubtedly permit a new generation of clinical trials that capitalize on the early success of immunotherapy for the treatment of NHL and, we hope, eventually provide safe and definitive treatments across the NHL spectrum.

Acknowledgements

P Armand gratefully acknowledges the generous and unwavering support of the Harold and Virginia Lash Foundation.

Footnote

Conflicts of Interest: CA Jacobson: consultancy for Kite, Novartis, Pfizer, Humanigen, Precision Biosciences, Celgene; P Armand: consultancy for BMS, Merck, Affimed, Pfizer, Infinity; research funding (institutional): BMS, Merck, Roche, Tensha, Affimed, Sequenta, Otsuka, Sigma Tau.

References

1. Mitchison NA. Studies on the immunological response to foreign tumor transplants in the mouse. I. The role of lymph node cells in conferring immunity by adoptive transfer. J Exp Med 1955;102:157-77.
2. Fyfe GA, Fisher RI, Rosenberg SA, et al. Long-term response data for 255 patients with metastatic renal cell carcinoma treated with high-dose recombinant interleukin-2 therapy. J Clin Oncol 1996;14:2410-1.
3. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17:2105-16.
4. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975;256:495-7.
5. Hanna MG Jr, Peters LC. Specific immunotherapy of established visceral micrometastases by BCG-tumor cell vaccine alone or as an adjunct to surgery. Cancer 1978;42:2613-25.
6. Rosenberg SA, Packard BS, Aebersold PM, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med 1988;319:1676-80.
7. Rosenberg SA, Yang JC, Sherry RM, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res 2011;17:4550-7.
8. Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically

engineered lymphocytes. Science 2006;314:126-9.
9. Robbins PF, Morgan RA, Feldman SA, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J Clin Oncol 2011;29:917-24.
10. Schulz C, Leuschen NV, Frohlich T, et al. Identification of novel downstream targets of platelet glycoprotein VI activation by differential proteome analysis: implications for thrombus formation. Blood 2010;115:4102-10.
11. Waterhouse P, Penninger JM, Timms E, et al. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. Science 1995;270:985-8.
12. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027-34.
13. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
14. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375-84.
15. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908-18.
16. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.
17. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018;378:439-48.
18. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377:2531-44.
19. Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood 2010;116:4099-102.
20. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol 2015;33:540-9.
21. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-8.
22. Zhao Z, Condomines M, van der Stegen SJC, et al. Structural Design of Engineered Costimulation Determines Tumor Rejection Kinetics and Persistence of CAR T Cells. Cancer Cell 2015;28:415-28.
23. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med 2017;377:2545-54.
24. Abramson J, Gordon LI, Palomba ML, et al. Updated safety and long term clinical outcomes in TRANSCENT NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. J Clin Oncol 2018;36:abstr 7505.
25. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-95.
26. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy for Acute Lymphoblastic Leukemia. Crit Care Med 2017;45:e124-31.
27. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med 2018;24:739-48.
28. Santomasso BD, Park JH, Salloum D, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. Cancer Discov 2018;8:958-71.
29. Gust J, Hay KA, Hanafi LA, et al. Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. Cancer Discov 2017;7:1404-19.
30. Taraseviciute A, Tkachev V, Ponce R, et al. Chimeric Antigen Receptor T Cell-Mediated Neurotoxicity in Nonhuman Primates. Cancer Discov 2018;8:750-63.
31. Giavridis T, van der Stegen SJC, Eyquem J, et al. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med 2018;24:731-8.
32. Sotillo E, Barrett DM, Black KL, et al. Convergence of Acquired Mutations and Alternative Splicing of CD19 Enables Resistance to CART-19 Immunotherapy. Cancer Discov 2015;5:1282-95.
33. Ruella M, Barrett DM, Kenderian SS, et al. Dual CD19 and CD123 targeting prevents antigen-loss relapses after CD19-directed immunotherapies. J Clin Invest 2016;126:3814-26.
34. Cherkassky L, Morello A, Villena-Vargas J, et al.

Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor-mediated inhibition. J Clin Invest 2016;126:3130-44.
35. Chong EA, Melenhorst JJ, Lacey SF, et al. PD-1 blockade modulates chimeric antigen receptor (CAR)-modified T cells: refueling the CAR. Blood 2017;129:1039-41.
36. Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 2018;24:563-71.
37. Kiyasu J, Miyoshi H, Hirata A, et al. Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma. Blood 2015;126:2193-201.
38. Challa-Malladi M, Lieu YK, Califano O, et al. Combined genetic inactivation of beta2-Microglobulin and CD58 reveals frequent escape from immune recognition in diffuse large B cell lymphoma. Cancer Cell 2011;20:728-40.
39. Yang ZZ, Novak AJ, Stenson MJ, et al. Intratumoral CD4+CD25+ regulatory T-cell-mediated suppression of infiltrating CD4+ T cells in B-cell non-Hodgkin lymphoma. Blood 2006;107:3639-46.
40. Riihijärvi S, Fiskvik I, Taskinen M, et al. Prognostic influence of macrophages in patients with diffuse large B-cell lymphoma: a correlative study from a Nordic phase II trial. Haematologica 2015;100:238-45.
41. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med 2004;351:2159-69.
42. Taskinen M, Karjalainen-Lindsberg ML, Nyman H, et al. A high tumor-associated macrophage content predicts favorable outcome in follicular lymphoma patients treated with rituximab and cyclophosphamide-doxorubicin-vincristine-prednisone. Clin Cancer Res 2007;13:5784-9.
43. Kiaii S, Clear AJ, Ramsay AG, et al. Follicular lymphoma cells induce changes in T-cell gene expression and function: potential impact on survival and risk of transformation. J Clin Oncol 2013;31:2654-61.
44. Pangault C, Ame-Thomas P, Ruminy P, et al. Follicular lymphoma cell niche: identification of a preeminent IL-4-dependent T(FH)-B cell axis. Leukemia 2010;24:2080-9.
45. Guilloton F, Caron G, Menard C, et al. Mesenchymal stromal cells orchestrate follicular lymphoma cell niche through the CCL2-dependent recruitment and polarization of monocytes. Blood 2012;119:2556-67.
46. Yang ZZ, Grote DM, Ziesmer SC, et al. PD-1 expression defines two distinct T-cell sub-populations in follicular lymphoma that differentially impact patient survival. Blood Cancer J 2015;5:e281.
47. Yang ZZ, Grote DM, Ziesmer SC, et al. IL-12 upregulates TIM-3 expression and induces T cell exhaustion in patients with follicular B cell non-Hodgkin lymphoma. J Clin Invest 2012;122:1271-82.
48. Wahlin BE, Aggarwal M, Montes-Moreno S, et al. A unifying microenvironment model in follicular lymphoma: outcome is predicted by programmed death-1--positive, regulatory, cytotoxic, and helper T cells and macrophages. Clin Cancer Res 2010;16:637-50.
49. Carreras J, Lopez-Guillermo A, Roncador G, et al. High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J Clin Oncol 2009;27:1470-6.
50. Richendollar BG, Pohlman B, Elson P, et al. Follicular programmed death 1-positive lymphocytes in the tumor microenvironment are an independent prognostic factor in follicular lymphoma. Hum Pathol 2011;42:552-7.
51. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116:3268-77.
52. Shi M, Roemer MG, Chapuy B, et al. Expression of programmed cell death 1 ligand 2 (PD-L2) is a distinguishing feature of primary mediastinal (thymic) large B-cell lymphoma and associated with PDCD1LG2 copy gain. Am J Surg Pathol 2014;38:1715-23.
53. Twa DD, Chan FC, Ben-Neriah S, et al. Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. Blood 2014;123:2062-5.
54. Eberle FC, Salaverria I, Steidl C, et al. Gray zone lymphoma: chromosomal aberrations with immunophenotypic and clinical correlations. Mod Pathol 2011;24:1586-97.
55. Chapuy B, Roemer MG, Stewart C, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. Blood 2016;127:869-81.
56. Green MR, Rodig S, Juszczynski P, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. Clin Cancer Res 2012;18:1611-8.

57. Panjwani PK, Charu V, DeLisser M, et al. Programmed death-1 ligands PD-L1 and PD-L2 show distinctive and restricted patterns of expression in lymphoma subtypes. Hum Pathol 2018;71:91-9.
58. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res 2013;19:3462-73.
59. Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. Blood 2017;129:3419-27.
60. He R, Ding W, Viswanatha DS, et al. PD-1 Expression in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) and Large B-cell Richter Transformation (DLBCL-RT): A Characteristic Feature of DLBCL-RT and Potential Surrogate Marker for Clonal Relatedness. Am J Surg Pathol 2018;42:843-54.
61. Wilcox RA, Feldman AL, Wada DA, et al. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood 2009;114:2149-58.
62. Lawrence MS, Stojanov P, Mermel CH, et al. Discovery and saturation analysis of cancer genes across 21 tumour types. Nature 2014;505:495-501.
63. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol 2016;34:2698-704.
64. Ansell S, Gutierrez ME, Shipp MA, et al. A phase I sutdy of nivolumab in combination with ipilimumab for relapsed or refractory hematologic malignancies (CheckMate 039). Blood 2016;128:183.
65. Ansell SM, Hurvitz SA, Koenig PA, et al. Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. Clin Cancer Res 2009;15:6446-53.
66. Berger R, Rotem-Yehudar R, Slama G, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. Clin Cancer Res 2008;14:3044-51.
67. Palomba ML, Till BG, Park SI, et al. A phase 1B study evaluating the safety and clinical activity of atezolizumab combined wtih obinutuzumab in patients with relapsed or refractory non-Hodgkin lymphoma (NHL). Hematol Oncol 2017;35:137.
68. Nastoupil L. WJ, Fowler NH, et al. High complete response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: results of an open-label, phase II study. Blood 2017;130:a414.
69. Gopal AK, Bartlett N, Levy R, et al. A phase I study of PF-05082566 (anti-4-1BB) + rituximab in patients with CD20+ NHL. J Clin Oncol 2015;33:3004.
70. Khodadoust M, Rook AH, Porcu P, et al. Pembrolizumab for treatment of relapsed/refractory mycosis fungoides and Sezary syndrome: clinical efficacy in a Citn multicenter phase 2 study. Blood 2016;128:181.
71. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood 2017;130:267-70.
72. Zinzani PL, Thieblemont C, Melnichenko V, et al. Efficacy and safety of pembrolizumab in relapsed/refractory primary mediastinal large B-cell lymphoma (rrPMBCL): updated analysis of the Keynote-170 phase 2 trial. Blood 2017;130:2833.
73. Melani C, Major A, Schowinsky J, et al. PD-1 Blockade in Mediastinal Gray-Zone Lymphoma. N Engl J Med 2017;377:89-91.
74. Nayak L, Iwamoto FM, LaCasce A, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. Blood 2017;129:3071-3.
75. Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood 2017;129:2437-42.
76. Advani R, Flinn I, Popplewell L, et al. Activity and tolerability of the first-in-class anti-CD47 antibody Hu549-G4 with rituximab in relapsed/refractory non-Hodgkin's lymphoma: initial Phase 1b/2 results. J Clin Oncol 2018;36:a7504.

doi: 10.21037/aol.2018.12.01
Cite this article as: Jacobson CA, Armand P. Immunotherapy in non-Hodgkin lymphoma. Ann Lymphoma 2018;2:9.

