**Name of Journal:** *World Journal of Stem Cells*

**Manuscript NO:** 64262

**Manuscript Type:** REVIEW

**Immunotherapy in the treatment of lymphoma**

Popovic LS *et al*. Immunotherapy in lymphoma

Lazar S Popovic, Gorana Matovina-Brko, Maja Popovic, Milica Popovic, Ana Cvetanovic, Ivan Nikolic, Biljana Kukic, Dragana Petrovic

**Lazar S Popovic, Maja Popovic, Ivan Nikolic, Biljana Kukic,** Department for Medical Oncology, Oncology Institute of Vojvodina, University of Novi Sad, Novi Sad 21000, Serbia

**Gorana Matovina-Brko, Dragana Petrovic,** Department for Medical Oncology, Oncology Institute of Vojvodina, Novi Sad 21000, Serbia

**Milica Popovic,** Department for Nephrology and Clinical Immunology, Clinical Center of Vojvodina, University of Novi Sad, Novi Sad 21000, Serbia

**Ana Cvetanovic,** Department for Medical Oncology, Clinical Center of Nis, University of Nis, Nis 18000, Serbia

**Author contributions:** Popovic LS, Matovina-Brko G and Popovic Ma performed the literature research and wrote the manuscript; Popovic LS, Matovina-Brko G and Popovic Ma, Popovic Mi, Cvetanovic A, Nikolic I, Kukic B, and Petrovic D analyzed the collected data; all authors have read and approved the final manuscript.

**Corresponding author: Lazar S Popovic, MD, PhD, Professor,** Department for Medical Oncology, Oncology Institute of Vojvodina, University of Novi Sad, Put dr Goldmana 4, Novi Sad 21000, Serbia. lazar.popovic@mf.uns.ac.rs

**Received:** February 13, 2021

**Revised:** March 31, 2021

**Accepted:** May 8, 2021

**Published online:**

**Abstract**

Relapsed or refractory non-Hodgkin’s lymphomas, especially diffuse large B-cell lymphoma as well as relapsed or refractory Hodgkin lymphomas are hard-to-treat diseases. Patients who do not respond to initial therapy or experience relapse are treated with salvage regimens, and if eligible for aggressive therapy, treatment is continued with high-dose chemotherapy and autologous stem cell transplantation. Current therapy options can cure substantial numbers of patients, however for some it is still an uncurable disease. Numerous new drugs and cell therapies are being investigated for the treatment of relapsed or refractory lymphomas. Different types of immunotherapy options have shown promising results, and some have already become the standard of care. Here, we review immunotherapy options for the treatment of lymphoma and discuss the results, positions, practical aspects, and future directions of different drugs and cellular therapies for the treatment of this disease.

**Key Words:** Immunotherapy; Receptors; Chimeric antigen; Antibodies; Monoclonal; Immunoconjugates; Hodgkin disease; Lymphoma; Large B-cell; Diffuse

Popovic LS, Matovina-Brko G, Popovic M, Popovic M, Cvetanovic A, Nikolic I, Kukic B, Petrovic D. Immunotherapy in the treatment of lymphoma. *World J Stem Cells* 2021; In press

**Core Tip:** Relapsed or refractory non-Hodgkin’s lymphomas, especially diffuse large B-cell lymphoma, are hard-to-treat diseases. Many immunotherapeutic options have changed the course of treatment for different solid tumors. Here, we discuss the results, positions, practical aspects, and future directions of different drugs and cellular therapies for the treatment of lymphoma.

**INTRODUCTION**

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma and accounts for approximately 30%-58% of cases. The combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) cures approximately 65% of patients[1]. Patients who do not respond to R-CHOP therapy or experience relapse are treated with one of the following salvage protocols: rituximab, cisplatin, cytarabine, and dexamethasone (R-DHAP) or rituximab, ifosfamide, carboplatin, and etoposide (R-ICE). If the patient responds and is eligible for aggressive therapy, treatment is continued with high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT)[2,3]. Approximately 20% of patients achieve survival with this procedure. Patients who are not eligible for HDCT usually receive second-line therapy with rituximab, gemcitabine and oxaliplatin (R-GEMOX) or rituximab and bendamustine (R-Benda), and a small percentage of these patients survive long-term[4,5]. Allogeneic stem cell transplantation (AlloSCT) is usually reserved for patients who have experienced two or more relapses of the disease. Approximately 20%-30% of patients achieve long-term remission but at the cost of high toxicity and treatment-related mortality[6].

The standard chemotherapy regimens doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (escBEACOPP) cure more than 80% of patients with classical Hodgkin’s lymphoma (cHL). Salvage chemotherapy followed by HDCT/ASCT in relapsed or refractory patients can cure another 50%. Brentuximab-vedotin and checkpoint inhibitors have already become the standard of care ahead of allogeneic transplantation in patients with R/R cHL because of their high efficacy and significantly lower toxicity than AlloSCT[7-12].

Numerous new drugs and cell therapies are being investigated for the treatment of R/R lymphomas. Different types of immunotherapy options have shown promising results, and some have already become the standard of care. Here, we review immunotherapy options for the treatment of lymphoma and the practical aspects of those therapies.

**IMMUNE MECHANISMS OF AVOIDING T-CELL RESPONSES IN LYMPHOMA**

The human immune system has two basic tasks. The first is to recognize and neutralize foreign cells, both microorganisms such as bacteria and viruses, and malignant cells. The second is to prevent excessive activation against and destruction of the body’s own cells to avoid the development of autoimmune phenomena and diseases[13]. Cellular infiltrates of lymphoma consist of malignant cells and various host immune system cells that significantly affect the onset and progression of malignant disease as well as the immune response against lymphoma[14,15]. For example, in cHL, only 1% of tumor infiltrates are malignant Reed-Sternberg cells[16]. The T-cell response is triggered by two consecutive signals. The first signal is T-cell activation *via* the T-cell receptor (TCR). This process occurs by the TCR binding to lymphoma cells and to the major histocompatibility complex (MHC) receptor, which is most commonly expressed on antigen-presenting cells (APCs). Another important signal is the binding of B7-1 and B7-2 receptors to APCs and the CD28 receptor on T cells. When those two steps are accomplished, effector T cells are activated, differentiated, and expanded[13,17]. However, there are several mechanisms by which lymphoma cells avoid effector T-cell recognition and destruction.

One way to avoid the response is to lose the expression of MHC class I and II molecules. Loss of class I MHC molecules occurs in approximately 75% of patients with aggressive lymphomas, while loss of class II MHC molecules is noted in approximately 30%[18]. Decreased class I MHC expression is associated with shorter progression-free survival (PFS) in patients with cHL[19]. Additionally, loss of class II MHC expression in immune-privileged sites in primary mediastinal lymphoma (PMLCL) and DLBCL leads to a lower objective response rate (ORR) and lower PFS[20,21].

Another barrier to the immune response is the expression of immunosuppressive proteins, which are so-called checkpoints, on both tumor cells and other immune cells within the tumor infiltrate. The physiological role of these receptors is to inhibit the autoimmune effects of T cells. The roles of programmed cell death receptor-1 (PD-1) and its ligands programmed cell death ligand 1 and 2 (PD-L1 and PD-L2)[13] have been most extensively studied. Effector T cells in the lymphoma infiltrate frequently express PD-1. The binding of PD-1 to PD-L1/2 receptors on both tumor cells and other cells of the immune system leads to T-cell exhaustion and apoptosis[13,22]. In addition to receptors of the PD-1 family, other less investigated checkpoints, such as TIGIT (T-cell immunoreceptor with Ig and ITIM domains), LAG-3 (lymphocyte-activation gene 3), and TIM-3 (T-cell immunoglobulin-3)[23], can modify the immune response and increase the complexity of the inhibition signaling network.

The third way the T-cell response is inhibited in lymphoma is the secretion of inhibitory cytokines by both malignant and immune cells[24-26]. Interleukin-10 (IL-10) levels are often elevated in patients with lymphoma and can potentially result in the expansion of myeloid-derived suppressive cells (MDSCs) that negatively affect the immune response[24]. IL-12, which initially stimulates the T-cell response but remains present, inhibits the T-cell response and reduces T-cell function[25]. Transforming growth factor β (TGFβ) activates a dysfunctional population of effector T cells, which also depletes the immune response[26].

Finally, the fourth mode of inhibition, which is closely related to cytokine stimulation and the immune signaling network, is the increased presence of suppressive and regulatory cells in the tumor infiltrate. MDSCs significantly inhibit T-cell proliferation and activation. Thus, the presence of a large number of these cells results in a reduced immune response against malignant cells[27]. In addition, macrophages and monocytes often express PD-L1 and PD-L2, and thus suppress the immune response by binding to the PD-1 receptor of T cells[28]. In addition to effector T cells, Fox3+ and CD25+ regulatory T cells are often found in the tumor infiltrate. Regulatory T cells play a role in controlling the immune response and are often responsible for the inadequate or suppressed immune response against malignant cells[29]. Lymphoma B-cells alone can induce Fox3 expression in CD4+ lymphocytes, and can thus promote the differentiation of suppressive T-cell clones[30].

**STRATEGIES FOR OVERCOMING INHIBITION OF THE IMMUNE RESPONSE IN LYMPHOMA**

There are several strategies for overcoming the mechanisms of immune response inhibition. The best known and most commonly used method, first used to treat various solid tumors and then in lymphomas, is the inhibition of PD-1 and PD-L1 binding with immune checkpoint inhibitor drugs. Blocking this checkpoint reduces the exhaustion of effector T cells and restores the ability of T cells to recognize and exterminate malignant cells[13].

Another strategy is the destruction of a malignant clone with an approach that is independent of APC presentation and does not rely on the MHC complex. Chimeric antigen receptor (CAR) T cells are produced by the *in vitro* engineering of a patient's T cells to render them capable of recognizing a specific antigen, such as malignant CD19-positive clones. CAR T cells act independently of MHC complexes and thus overcome resistance dependent on T-cell signaling pathways[31].

The third method is the direct engagement of CD3/CD16 effector immune cells with bispecific antibodies. One end of these antibodies binds to the CD19 receptor on B-lymphoma cells, and the other end binds to the CD3 receptor on T cells or the CD16 receptor on natural killer cells, thus causing a direct stimulation of the immune system and destruction of the malignant clone[32,33]. Direct inhibition of MDSCs is being investigated for the treatment of solid tumors and might also be a way to enhance the immune response in lymphomas[34].

**MONOCLONAL ANTIBODIES**

The anti-CD20 antibody rituximab was the first therapeutic antibody approved in oncology in the late 20th century. This drug changed the landscape and prognosis of almost all B-cell lymphoproliferative diseases and became the gold standard of treatment[35-38]. Attempts to improve the efficacy of CD20 antibodies have been intensively investigated with two new genetically engineered drugs, atumumab and obinutuzumab (Table 1). Ofatumumab is a humanized type I monoclonal antibody tested in a variety of B-cell lymphomas but to date has only been approved for the treatment of R/R chronic lymphocytic leukemia[39]. The type II antibody obinutuzumab has had greater success. The key difference between rituximab and obinutuzumab is the higher affinity of obinutuzumab for FcγRIII receptors on effector immune cells and the decreased FcγRIIb-mediated internalization of the CD20 receptor into lipid rafts, thus increasing antibody-dependent cellular cytotoxicity (ADCC)[40,41]. The CLL11 study demonstrated longer PFS when obinutuzumab was combined with chlorambucil (O-Clb) *vs* rituximab-chlorambucil (R-Clb). At that time, no difference in overall survival (OS) was shown[42]. n an updated analysis with a longer follow-up, O-Clb extended OS relative to R-Clb with no new safety issues[43]. The GALLIUM study compared obinutuzumab with rituximab in combination with chemotherapy in untreated patients with follicular lymphoma (FL). Obinutuzumab achieved a superior PFS without an OS benefit compared with rituximab[44]. In patients refractory to rituximab, obinutuzumab also showed benefit in the GADOLIN study. The combination of O-bendamustin prolonged PFS over bendamustin monotherapy[45]. Unlike chronic lymphocytic leukemia (CLL) and FL, obinutuzumab showed no benefit compared with rituximab in combination with CHOP chemotherapy in patients with DLBCL[46].

CD19 is a receptor present in B-cell lymphoma, and is an interesting target for drug development. Tafasitamab is a humanized antibody against the CD19 receptor. Similar to obinutuzumab, tafasitamab has a strong affinity for binding FcγRIII receptors to effector cells of the immune system, and is thus a potent ADCC inducer. In a phase IIa study, single-agent tafasitamab had an ORR of 26% in pretreated patients with DLBCL[47]. In a phase II study of L-MIND in R/R DLBCL, tafasitamab in combination with lenalidomide had an ORR of 54%, with 32% of patients achieving a complete response (CR)[48]. A phase II/III B-MIND study comparing the combination of tafasitamab-benda with R-Benda in R/R DLBCL and a phase III study comparing R-CHOP with tafasitamab and lenalidomide as first-line treatment of B-cell non-Hodgkin lymphoma(B-NHL)[49,50] are underway.

Magrolimab is a humanized monoclonal antibody that binds to the CD47 receptor that is often expressed in B-cell lymphomas. Unlike CD19 and CD20 antibodies, the magrolimab mechanism of action is not related to the direct killing of malignant cells, ADCC, or cell-dependent cytotoxicity. The SIRPα receptor of macrophages binds to CD47, leading to macrophage invasion and a reduction in the immune response. Magrolimab, by binding to CD47, prevents the binding of SIRPα macrophages to this receptor and thus increases the recognition and destruction of lymphoma cells[51]. In phase Ib/II recruiting a heavily pretreated population of DLBCL and FL patients, magrolimab showed an ORR of 50% and a CR of 36% without significant toxicity[52]. Mogamulizumab is an antibody against C chemokine receptor 4 (CCR4). In a phase III study in cutaneous T-cell lymphomas (CTCLs), mogamulizumab demonstrated a longer PFS than vorinostat[53].

**ANTIBODY-DRUG CONJUGATES**

Attempts to increase the effectiveness of antibodies led to the construction of molecules with radioactive elements, such as yttrium-90 (ibrotumab-tiuxetan)[54] and iodine-131 (tositumomab)[55], and more recently, cytotoxic agents (Table 2).

Brentuximab vedotin (BV) is a CD30-targeting antibody-drug conjugate (ADC) that includes the cytotoxic agent monomethylauristatin B on its Fc fragment[56]. BV was first approved for the treatment of cHL and systemic anaplastic large-cell lymphoma (sALCL). Tumor reduction was observed in 86% of 46 patients in a phase I study[57]. Another cohort of 102 patients with R/R cHL was treated with BV. Those patients had previously received at least two lines of therapy or HDCT/ASCT. The ORR was 75% with a CR of 34%. The median PFS and the duration of response in those who achieved CR were 5.6 and 20.5 mo, respectively[10,58]. The AETHERA study evaluated BV maintenance after HDCT/ASCT in patients with a high risk of relapse after ASCT, defined as relapse within 12 mo of initial therapy, primary refractory disease, and/or extranodal presentation. A total of 329 patients were randomized to BV or a placebo. The median PFS was 49.2 mo with BV *vs* 24.1 mo with the placebo (HR 0.57, *P* = 0.0013)[59]. After 5 years of follow-up, the analysis was updated to reveal that relapse-free survival was 59% in patients who received BV and 41% in those given the placebo. The OS difference has not yet been determined, but the need for further treatment in BV-treated patients was reduced[60]. Another study compared six cycles of BV in combination with AVD with six cycles of ABVD therapy alone in patients with stage III and IV untreated cHL. After 2 years of follow-up, 82.1% of patients in the BV arm and 77.2% in the control arm were progression free (HR 0.77, *P* = 0.04)[61]. In recent years, BV has also played an important role in the treatment of CD30-positive T-cell lymphomas. The ALCANZA study compared BV with the investigators’ choice of methotrexate or bexarotene in R/R CTCLs. The primary endpoint was the 4-mo objective response (ORR4). The ORR4 was 56.3% in the BV 12.5% in the control arm (*P* < 0.0001)[62]. BV has shown remarkable results for the treatment of R/R ALCL[63]. However, probably the greatest progress made using BV has been in the initial treatment of CD30-positive peripheral T-cell lymphomas. The randomized, double-blind, phase III ECHELON-2 study randomized a total of 601 patients to BV + CHP (A-CHP) or CHOP therapy. The median PFS in the A-CHP arm was 48.2 mo compared with 20.8 mo in the CHOP arm (HR 0.71 *P* = 0.011). BV also prolonged OS in comparison to the control (HR 0.66, *P* = 0.0244)[64]. The most common toxicity associated with BV is peripheral sensory neuropathy, which is reversible in most cases[56-64].

Polatuzumab vedotin (PV) is an ADC that targets the CD79b receptor expressed on B-cell lymphomas. PV was approved by the Food and Drug Administration (FDA) based on the results of a phase II study in R/R DLBCL. In that study, the addition of PV was compared with the R-Benda combination. Compared with patients receiving R-Benda, patients receiving PV had a longer median PFS (9.5 mo *vs* 3.7 mo; HR 0.36, *P* = 0.001), a longer OS (12.4 mo *vs* 4.7 mo; HR 0.42, *P* = 0.002), and a higher CR rate (40% *vs* 17.5%; *P* = 0.026)[65]. Two important clinical trials are underway to further investigate the efficacy of PV for lymphoma, including PV in R/R FL and DLBCL in combination with lenalidomide, and PV as the first-line treatment of the DLBCL with an International Prognostic Index (IPI) score of 2-5 in combination with R-CHOP therapy in the phase III POLARIX study[66,67]. Moxetumomab pseudotox was approved for the treatment of R/R hairy cell leukemia (HCL) based on a phase II study in which 30% of patients with HCL who had previously received at least two lines of treatment achieved CR[68].

**BISPECIFIC ANTIBODIES/BISPECIFIC T-CELL ENGAGERS**

Bispecific antibodies/bispecific T-cell engagers (BITEs) bind two antigens/receptors. One is found on a malignant cell and the other is most often CD3, which is a T-cell surface antigen. In that way, the molecules mediate the direct destruction of lymphoma cells by T cells (Table 3). Blinatumomab is a CD19/CD3 antibody approved for the treatment of R/R B-cell acute lymphoblastic leukemia (B-ALL)[69]. Blinatumomab was tested as a therapy for R/R DLBCL in a phase I trial[70]. A high rate of neurotoxicity was noted, and the drug did not enter the later clinical trial stages. Long-term follow-up data from those patients have been recently published. The median OS was 7.7 years in patients receiving a dose ≥ 60 μg/m2, indicating that this approach might be an important consideration for future research[71].

Mosunetuzumab is a BITE targeting CD20/CD3. It has a longer serum half-life than blinatumomab because of its pharmacological properties and does not have to be administered as a multiday continuous infusion. In a population of heavily pretreated patients with R/R FL and R/R DLBCL, including those who relapsed after CAR T-cell therapy, mosunetuzumab achieved ORRs of 64.1% and 42.2%, respectively, in indolent and aggressive lymphomas. The CR rate was 18.6% for DLBCL and 34.7% for FL. The most limiting blinatumomab and CAR T-cell toxicities were neurotoxicity in 44% and cytokine releasing syndrome (CRS) in 28.4% of patients with mosunetuzumab, mostly grade 1 or 2[72]. REG1979 and CD20-TBC are two CD20/CD3 BITEs that have been tested in phase I studies[73-75]. CD20-TBC achieved a 47% ORR and 34% CR in heavily pretreated NHL patients. The incidence of CRS was 55% and was mostly grade 1 or 2[75].

**CHECKPOINT INHIBITORS**

Checkpoint inhibitors (CPIs, Table 4) have revolutionized the treatment of solid tumors and have become the absolute standard of care for melanoma, lung cancer, urological tumors, and triple-negative breast cancer[76-83]. The rationale for CPI clinical trials for cHLis is high PD-L1/PD-L2 expression as a result of copy-number amplification of the PD-L1 and JAK gene loci on chromosome 9p24[16]. Nivolumab and pembrolizumab have shown good results in heavily pretreated patients with R/R cHL. Nivolumab achieved an ORR of 69%, a CR of 40%, and a median DoR of 16.6 mo in patients who relapsed after HDCT/ASCT[84]. Similar to nivolumab, pembrolizumab achieved an ORR of 69%, 22% CR, a 6-mo PFS of 72.4%, and an OS of 99.5%[85]. The KEYNOTE-204 study compared pembrolizumab with BV in patients who had previously relapsed after HDCT/ASCT or who were not suitable for ASCT. That phase III study included a total of 304 patients. The primary endpoint, median PFS, was longer in the pembrolizumab arm (13.2 mo *vs* 8.3 mo; HR 0.65, *P* = 0.00271). Pembrolizumab had demonstrated benefits in all subgroups of patients with primary refractory disease, including those who previously had ASCT or had previously been treated with BV[86]. Nivolumab is being studied in previously untreated patients with stage III and IV cHL. The study compares nivolumab and BV in combination with doxorubicin, vinblastine and dacarbazine (AVD) chemotherapy[87].

Nivolumab has also been studied in combination with BV and/or ipilimumab in patients with R/R cHL. The Nivo + BV combination was tested as salvage treatment in a phase I/II trial, after which patients could proceed to ASCT. Therapy was given for up to four cycles. The CR rate was 61% and the ORR 82%. Fewer than 10% of the patients received corticosteroids because of adverse events, and stem cell collection was not compromised[88]. The combination of Nivo + BV, ipilimumab + BV, and triple therapy with Nivo + Ipi + BV was investigated in phase I of the study. The ORRs were 89%, 76%, and 82%, respectively, but grade 3 and higher adverse events were observed in 16%, 43%, and 50% of patients, respectively[89].

In NHL, unlike in cHL, CPIs have not shown a high level of response. Only in PMBCL, a subtype of DLBCL, does response to CPI occur, because PMBCL shares some features with cHL and expresses PD-L1[91]. Pembrolizumab achieved an ORR of 45%, with a median DoR not reached after 1 year of follow-up in the KEYNOTE-170 study. The CR rate was 13%[91]. Pembrolizumab also achieved a response rate of 38% in patients with R/R CTCL[92].

**CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY**

Chimeric antigen receptor T cells are therapies involving the *in vitro* genetic engineering of patient T cells capable of recognizing and killing CD19-positive B-lymphoma cells. CAR T cells consist of an extracellular variable fragment targeted to tumors, a hinge antigen-transmembrane region, and an intracellular domain. The development of CAR T cells began with a first-generation receptor that consisted of the CD3ζ signaling domain and had limited persistence and efficacy. The addition of a costimulatory domain to second-generation CAR T-cell receptors led to greater efficacy. The most important feature of CAR T-cell action is that it does not depend on MHC costimulation and acts by activating T-cell signals and costimulatory pathways (Table 5)[31,93,94].

Two CAR T-cell products have been approved by the FDA in the absence of randomized trials, based on comparison with the historical data on R/R DLBCL treatment[95]. The axicabtagene-lisoleucel (axi-cel) CAR T-cell receptor expresses the CD28 costimulatory domain and was examined in a phase 2 trial in patients with R/R DLBCL. One hundred-eleven patients were included in the study. The production of CAR T cells was successful in 110 patients, and the therapy was applied in 101 patients. The ORR was 82%, with a CR rate of 54%. After a median follow-up of 15.4 mo, 42% of the patients were still without progression, and 40% were still in complete remission. The total 18-mo survival was 52%. The most common side effects were cytopenias, while CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) of grade 3 and higher occurred in 13% and 28% of patients, respectively[96]. Tisagenlecleucel (tisa-cel) is a CAR T-cell product, similar to axi-cel, directed against the CD19 antigen of B-cell lymphomas but with a different 4-1BB costimulatory domain. Tisa-cel showed an ORR of 52%, of which 40% achieved CR in a study of 93 patients with R/R DLBCL. After 12 mo of follow-up, 65% of patients were progression free, 79% of whom achieved CR[97]. Lisocabtagen-maraleucel (liso-cel) is another anti-CD19 4-1BB CAR T-cell product that has shown significant results in R/R DLBCL. The study included 344 patients who underwent leukapheresis, of whom 269 received at least one dose of liso-cel. Almost all patients (97%) had previously received at least two lines of therapy, 42% were older than 65 years of age, 67% had chemotherapy-refractory disease, and seven had secondary CNS involvement. The overall response was 73%, with 53% of patients achieving CR. Grade 3 and higher chronic inflammatory response syndrome (CIRS) and ICANS occurred in 2% and 10% of patients, respectively[98].

CAR T-cell therapies have also been shown to be effective for mantle cell lymphoma (MCL) and CLL in addition to DLBCL. Brexucabtagene-autoleucel was investigated in pretreated patients with MCL. The ORR was 93%, and the CR rate was 67%. The 1-year PFS rate was 61%. The toxicity profile was similar to that of other CAR T-cell products tested for DLBCL[99]. CLL is one of the first diseases in which CAR T-cell therapy was tested. Tisa-cel and liso-cel had substantial and long-lasting responses in R/R CLL[100,101]. Similar studies have shown a high ORR and long remission after CAR T-cell therapy in patients with FL, marginal zone lymphoma (MZL), and Epstein-Bar virus (EBV)-associated lymphoma[102-104].

The application of CAR T cells is complex and requires careful patient selection and a series of procedures from leukapheresis, bridging therapy, laboratory treatment, lymphodepletion, and infusion of the CAR T-cell product to the management of acute and chronic toxicities[93]. Clinical studies with axi-cel and tisa-cel included fit patients (ECOG 0-1)[96,97]. Analysis of real-world data showed that patients with poorer performance status could also be treated successfully[105]. Some patients are not eligible for this type of therapy and are excluded from clinical trials, including those with renal impairment (creatinine clearance < 40), liver or lung damage, or a left ventricular ejection fraction < 40%)[96-98,105]. Patients with neurological diseases or cognitive impairment are also not eligible for this type of therapy[105]. The DLBCL subtype did not affect the ORR[96,97]. Although CAR T cells have not been registered for the treatment of DLBCL with CNS involvement, several studies that included such patients have shown CAR T-cell efficacy in this group. On the other hand, patients with high disease volume and high lactate dehydrogenase (LDH) have shorter PFS times[105]. Some patients need bridging therapy after leukapheresis because of the aggressiveness of the disease and the 4-6 wk it takes to make a CAR T-cell product. This therapy may include the R-ICE or R-DHAP protocols[2] as well as the combination of polatuzumab with rituximab and bendamustine[65].

CAR T cells have two specific toxicities in addition to pancytopenia, febrile neutropenia, and infections, which are CRS and ICANS. CRS is characterized by high fever, but as the clinical condition progresses, capillary leak syndrome, hypotension, and hypoxia of varying degrees occur. Any organ in the body can be affected[106,107]. On the other hand, ICANS is characterized by various neurological symptoms, including decreased level of consciousness, motor dysfunction, and speaking difficulties. The progression of symptoms can lead to convulsions and cerebral edema[106]. Tocilizumab, an anti-IL-6 antibody, is used to treat those symptoms. In addition to tocilizumab, corticosteroid therapy has shown results in ICANS therapy[106,107]. Clinical trials are underway with various drugs, including tocilizumab, corticosteroids, and anakinra, in an attempt to provide prophylaxis for CRS and ICANS after CAR T-cell therapy[108,109].

**CONCLUSION**

***Are we going to replace stem cell transplantation with immunotherapy?***

Relapsed or refractory DLBCL has a poor prognosis. The SCHOLAR-1 study showed that the median survival time of refractory disease was 6.3 mo[95]. The median survival time was approximately 13 mo in our patients, and a large number of patients were not eligible for HDCT/ASCT because of refractory disease or poor performance status[110]. HDCT/ASCT for fit patients remains the standard of care, but many patients are not eligible for that procedure, and some relapse after ASCT. Tafasitamab and selinexor have shown promising results, but PV in combination with rituximab and bendamustine has been largely adopted as the standard of care. We are waiting for the results of clinical trials investigating polatuzumab and tafasitamab in the initial treatment of DLBCL[50,67]. Despite the complexity of the CAR T-cell procedure itself, the results obtained with CAR T-cell therapy have pushed AlloSCT to later lines of therapy, and three studies comparing different CD19 CAR T cells with HDCT/ASCT are underway[111-113]. Mosunetuzumab and other BITEs have shown promising results in the early stages of research and are a potential therapeutic option after relapse following CAR T-cell therapy or in countries where CAR T cells are not available. CRS and ICANS are potentially fatal complications of both CAR T-cell therapy and BITE, and significant education is needed in terms of recognizing and treating these complications.

Hodgkin's lymphoma is a curable disease in over 80% of cases. HDCT/ASCT is an important part of relapse treatment. Most patients are eligible for that type of treatment, and the procedure can cure approximately 50% of patients[7-9]. BV improved treatment outcomes in patients with stage III and IV cHL and prolonged PFS when administered after HDCT/ASCT was given as maintenance therapy in patients at a high risk of relapse[59,61]. AlloSCT has also been significantly suppressed by the CPI of pembrolizumab and nivolumab, which are now standard fourth-line treatments. Pembrolizumab has achieved even longer PFS and OS than brentuximab-vedotin[86] and is slowly becoming the first treatment option after disease progression following ASCT. Promising results achieved by the combination of BV and nivolumab provide optimism for the results achieved with this type of treatment. The results of first-line studies comparing nivolumab with chemotherapy and BV with chemotherapy[87,88].

**REFERENCES**

1 **Tilly H**, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26 Suppl 5**: v116-v125 [PMID: 26314773 DOI: 10.1093/annonc/mdv304]

2 **Hagberg H**, Gisselbrecht C; CORAL study group. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. *Ann Oncol* 2006; **17** Suppl 4: iv31-iv32 [PMID: 16702182 DOI: 10.1093/annonc/mdj996]

3 **Philip T**, Chauvin F, Bron D, Guglielmi C, Hagenbeek A, Coiffier B, Gisselbrecht C, Kluin Nelemans JC, Somers R, Misset JC. PARMA international protocol: pilot study on 50 patients and preliminary analysis of the ongoing randomized study (62 patients). *Ann Oncol* 1991; **2** Suppl 1: 57-64 [PMID: 2043500 DOI: 10.1093/annonc/2.suppl\_1.57]

4 **El Gnaoui T**, Dupuis J, Belhadj K, Jais JP, Rahmouni A, Copie-Bergman C, Gaillard I, Diviné M, Tabah-Fisch I, Reyes F, Haioun C. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. *Ann Oncol* 2007; **18**: 1363-1368 [PMID: 17496309 DOI: 10.1093/annonc/mdm133]

5 **Arcari A**, Chiappella A, Spina M, Zanlari L, Bernuzzi P, Valenti V, Tani M, Marasca R, Cabras MG, Zambello R, Santagostino A, Ilariucci F, Carli G, Musto P, Savini P, Marino D, Ghio F, Gentile M, Cox MC, Vallisa D. Safety and efficacy of rituximab plus bendamustine in relapsed or refractory diffuse large B-cell lymphoma patients: an Italian retrospective multicenter study. *Leuk Lymphoma* 2016; **57**: 1823-1830 [PMID: 26666433 DOI: 10.3109/10428194.2015.1106536]

6 **Modi D**, Kim S, Surapaneni M, Deol A, Alavi A, Ayash L, Ratanatharathorn V, Uberti JP; Long Term Outcomes of Allogeneic Transplant in Diffuse Large B-Cell Lymphoma. *Blood* 2018; **132**: 5769 [doi: 10.1182/blood-2018-99-114278]

7 **Eichenauer DA**, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, Engert A, Ladetto M; ESMO Guidelines Committee. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29**: iv19-iv29 [PMID: 29796651 DOI: 10.1093/annonc/mdy080]

8 **Schmitz N**, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, Boissevain F, Zschaber R, Müller P, Kirchner H, Lohri A, Decker S, Koch B, Hasenclever D, Goldstone AH, Diehl V; German Hodgkin's Lymphoma Study Group; Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* 2002; **359**: 2065-2071 [PMID: 12086759 DOI: 10.1016/S0140-6736(02)08938-9]

9 **Sibon D**, Morschhauser F, Resche-Rigon M, Ghez D, Dupuis J, Marçais A, Deau-Fischer B, Bouabdallah R, Sebban C, Salles G, Brice P. Single or tandem autologous stem-cell transplantation for first-relapsed or refractory Hodgkin lymphoma: 10-year follow-up of the prospective H96 trial by the LYSA/SFGM-TC study group. *Haematologica* 2016; **101**: 474-481 [PMID: 26721893 DOI: 10.3324/haematol.2015.136408]

10 **Gopal AK**, Chen R, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, Connors JM, Engert A, Larsen EK, Chi X, Sievers EL, Younes A. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. *Blood* 2015; **125**: 1236-1243 [PMID: 25533035 DOI: 10.1182/blood-2014-08-595801]

11 **Ansell SM**, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattry D, Freeman GJ, Rodig SJ, Chapuy B, Ligon AH, Zhu L, Grosso JF, Kim SY, Timmerman JM, Shipp MA, Armand P. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015; **372**: 311-319 [PMID: 25482239 DOI: 10.1056/NEJMoa1411087]

12 **Todisco E**, Castagna L, Sarina B, Mazza R, Anastasia A, Balzarotti M, Banna G, Tirelli U, Soligo D, Santoro A. Reduced-intensity allogeneic transplantation in patients with refractory or progressive Hodgkin's disease after high-dose chemotherapy and autologous stem cell infusion. *Eur J Haematol* 2007; **78**: 322-329 [PMID: 17253967 DOI: 10.1111/j.1600-0609.2007.00814.x]

13 **Chen DS**, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013; **39**: 1-10 [PMID: 23890059 DOI: 10.1016/j.immuni.2013.07.012]

14 **Tarte K**. Role of the microenvironment across histological subtypes of NHL. *Hematology Am Soc Hematol Educ Program* 2017; **2017**: 610-617 [PMID: 29222311 DOI: 10.1182/asheducation-2017.1.610]

15 **Kline J**, Godfrey J, Ansell SM. The immune landscape and response to immune checkpoint blockade therapy in lymphoma. *Blood* 2020; **135**: 523-533 [PMID: 31790142 DOI: 10.1182/blood.2019000847]

16 **Aoki T**, Chong LC, Takata K, Milne K, Hav M, Colombo A, Chavez EA, Nissen M, Wang X, Miyata-Takata T, Lam V, Viganò E, Woolcock BW, Telenius A, Li MY, Healy S, Ghesquiere C, Kos D, Goodyear T, Veldman J, Zhang AW, Kim J, Saberi S, Ding J, Farinha P, Weng AP, Savage KJ, Scott DW, Krystal G, Nelson BH, Mottok A, Merchant A, Shah SP, Steidl C. Single-Cell Transcriptome Analysis Reveals Disease-Defining T-cell Subsets in the Tumor Microenvironment of Classic Hodgkin Lymphoma. *Cancer Discov* 2020; **10**: 406-421 [PMID: 31857391 DOI: 10.1158/2159-8290.CD-19-0680]

17 **Alegre ML**, Frauwirth KA, Thompson CB. T-cell regulation by CD28 and CTLA-4. *Nat Rev Immunol* 2001; **1**: 220-228 [PMID: 11905831 DOI: 10.1038/35105024]

18 **Rimsza LM**, Roberts RA, Miller TP, Unger JM, LeBlanc M, Braziel RM, Weisenberger DD, Chan WC, Muller-Hermelink HK, Jaffe ES, Gascoyne RD, Campo E, Fuchs DA, Spier CM, Fisher RI, Delabie J, Rosenwald A, Staudt LM, Grogan TM. Loss of MHC class II gene and protein expression in diffuse large B-cell lymphoma is related to decreased tumor immunosurveillance and poor patient survival regardless of other prognostic factors: a follow-up study from the Leukemia and Lymphoma Molecular Profiling Project. *Blood* 2004; **103**: 4251-4258 [PMID: 14976040 DOI: 10.1182/blood-2003-07-2365]

19 **Roemer MG**, Advani RH, Redd RA, Pinkus GS, Natkunam Y, Ligon AH, Connelly CF, Pak CJ, Carey CD, Daadi SE, Chapuy B, de Jong D, Hoppe RT, Neuberg DS, Shipp MA, Rodig SJ. Classical Hodgkin Lymphoma with Reduced β2M/MHC Class I Expression Is Associated with Inferior Outcome Independent of 9p24.1 Status. *Cancer Immunol Res* 2016; **4**: 910-916 [PMID: 27737878 DOI: 10.1158/2326-6066.CIR-16-0201]

20 **Roberts RA**, Wright G, Rosenwald AR, Jaramillo MA, Grogan TM, Miller TP, Frutiger Y, Chan WC, Gascoyne RD, Ott G, Muller-Hermelink HK, Staudt LM, Rimsza LM. Loss of major histocompatibility class II gene and protein expression in primary mediastinal large B-cell lymphoma is highly coordinated and related to poor patient survival. *Blood* 2006; **108**: 311-318 [PMID: 16543468 DOI: 10.1182/blood-2005-11-4742]

21 **Booman M**, Douwes J, Glas AM, Riemersma SA, Jordanova ES, Kok K, Rosenwald A, de Jong D, Schuuring E, Kluin PM. Mechanisms and effects of loss of human leukocyte antigen class II expression in immune-privileged site-associated B-cell lymphoma. *Clin Cancer Res* 2006; **12**: 2698-2705 [PMID: 16675561 DOI: 10.1158/1078-0432.CCR-05-2617]

22 **Roemer MG**, Advani RH, Ligon AH, Natkunam Y, Redd RA, Homer H, Connelly CF, Sun HH, Daadi SE, Freeman GJ, Armand P, Chapuy B, de Jong D, Hoppe RT, Neuberg DS, Rodig SJ, Shipp MA. PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. *J Clin Oncol* 2016; **34**: 2690-2697 [PMID: 27069084 DOI: 10.1200/JCO.2016.66.4482]

23 **Anderson AC**, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: Co-inhibitory Receptors with Specialized Functions in Immune Regulation. *Immunity* 2016; **44**: 989-1004 [PMID: 27192565 DOI: 10.1016/j.immuni.2016.05.001]

24 **Xiu B**, Lin Y, Grote DM, Ziesmer SC, Gustafson MP, Maas ML, Zhang Z, Dietz AB, Porrata LF, Novak AJ, Liang AB, Yang ZZ, Ansell SM. IL-10 induces the development of immunosuppressive CD14(+)HLA-DR(low/-) monocytes in B-cell non-Hodgkin lymphoma. *Blood Cancer J* 2015; **5**: e328 [PMID: 26230952 DOI: 10.1038/bcj.2015.56]

25 **Yang ZZ**, Grote DM, Ziesmer SC, Niki T, Hirashima M, Novak AJ, Witzig TE, Ansell SM. 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**: 1271-1282 [PMID: 22426209 DOI: 10.1172/JCI59806]

26 **Yang ZZ**, Grote DM, Xiu B, Ziesmer SC, Price-Troska TL, Hodge LS, Yates DM, Novak AJ, Ansell SM. TGF-β upregulates CD70 expression and induces exhaustion of effector memory T cells in B-cell non-Hodgkin's lymphoma. *Leukemia* 2014; **28**: 1872-1884 [PMID: 24569779 DOI: 10.1038/leu.2014.84]

27 **Azzaoui I**, Uhel F, Rossille D, Pangault C, Dulong J, Le Priol J, Lamy T, Houot R, Le Gouill S, Cartron G, Godmer P, Bouabdallah K, Milpied N, Damaj G, Tarte K, Fest T, Roussel M. T-cell defect in diffuse large B-cell lymphomas involves expansion of myeloid-derived suppressor cells. *Blood* 2016; **128**: 1081-1092 [PMID: 27338100 DOI: 10.1182/blood-2015-08-662783]

28 **Carey CD**, Gusenleitner D, Lipschitz M, Roemer MGM, Stack EC, Gjini E, Hu X, Redd R, Freeman GJ, Neuberg D, Hodi FS, Liu XS, Shipp MA, Rodig SJ. Topological analysis reveals a PD-L1-associated microenvironmental niche for Reed-Sternberg cells in Hodgkin lymphoma. *Blood* 2017; **130**: 2420-2430 [PMID: 28893733 DOI: 10.1182/blood-2017-03-770719]

29 **Vardhana S**, Younes A. The immune microenvironment in Hodgkin lymphoma: T cells, B cells, and immune checkpoints. *Haematologica* 2016; **101**: 794-802 [PMID: 27365459 DOI: 10.3324/haematol.2015.132761]

30 **Yang ZZ**, Novak AJ, Ziesmer SC, Witzig TE, Ansell SM. CD70+ non-Hodgkin lymphoma B cells induce Foxp3 expression and regulatory function in intratumoral CD4+CD25 T cells. *Blood* 2007; **110**: 2537-2544 [PMID: 17615291 DOI: 10.1182/blood-2007-03-082578]

31 **Kallam A**, Vose JM. Recent Advances in CAR-T Cell Therapy for Non-Hodgkin Lymphoma. *Clin Lymphoma Myeloma Leuk* 2019; **19**: 751-757 [PMID: 31648957 DOI: 10.1016/j.clml.2019.09.598]

32 **Viardot A**, Goebeler ME, Hess G, Neumann S, Pfreundschuh M, Adrian N, Zettl F, Libicher M, Sayehli C, Stieglmaier J, Zhang A, Nagorsen D, Bargou RC. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. *Blood* 2016; **127**: 1410-1416 [PMID: 26755709 DOI: 10.1182/blood-2015-06-651380]

33 **Rothe A**, Sasse S, Topp MS, Eichenauer DA, Hummel H, Reiners KS, Dietlein M, Kuhnert G, Kessler J, Buerkle C, Ravic M, Knackmuss S, Marschner JP, Pogge von Strandmann E, Borchmann P, Engert A. A phase 1 study of the bispecific anti-CD30/CD16A antibody construct AFM13 in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 2015; **125**: 4024-4031 [PMID: 25887777 DOI: 10.1182/blood-2014-12-614636]

34 **Tomzcak P**, Popovic L, Barhelemy P, Janicic A, Fernandez ES, Borchiellini D, Aglietta M, Maroto J, Carnot A, O'Connell B, Zizlsperger N, Zhang HH, Valderrama BP. Preliminary Analysis of a Phase 2, Multicenter, Randomized, Active-Control Study to Evaluate the Efficacy and Safety of Eganelisib (IPI-549) in Combination with Nivolumab compared to Nivolumab Monotherapy in Patients with Advanced Urothelial Carcinoma. *J Clin Oncol* 2021 **39**: 436-436 [DOI: 10.1200/JCO.2021.39.6\_suppl.436]

35 **Coiffier B**, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; **346**: 235-242 [PMID: 11807147 DOI: 10.1056/NEJMoa011795]

36 **Pfreundschuh M**, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, Ma D, Gill D, Walewski J, Zinzani PL, Stahel R, Kvaloy S, Shpilberg O, Jaeger U, Hansen M, Lehtinen T, López-Guillermo A, Corrado C, Scheliga A, Milpied N, Mendila M, Rashford M, Kuhnt E, Loeffler M; MabThera International Trial Group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006; **7**: 379-391 [PMID: 16648042 DOI: 10.1016/S1470-2045(06)70664-7]

37 **Salles G**, Mounier N, de Guibert S, Morschhauser F, Doyen C, Rossi JF, Haioun C, Brice P, Mahé B, Bouabdallah R, Audhuy B, Ferme C, Dartigeas C, Feugier P, Sebban C, Xerri L, Foussard C. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood* 2008; **112**: 4824-4831 [PMID: 18799723 DOI: 10.1182/blood-2008-04-153189]

38 **Fischer K**, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P, Langerbeins P, von Tresckow J, Engelke A, Maurer C, Kovacs G, Herling M, Tausch E, Kreuzer KA, Eichhorst B, Böttcher S, Seymour JF, Ghia P, Marlton P, Kneba M, Wendtner CM, Döhner H, Stilgenbauer S, Hallek M. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood* 2016; **127**: 208-215 [PMID: 26486789 DOI: 10.1182/blood-2015-06-651125]

39 **Wierda WG**, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, Robak T, Furman RR, Hillmen P, Trneny M, Dyer MJ, Padmanabhan S, Piotrowska M, Kozak T, Chan G, Davis R, Losic N, Wilms J, Russell CA, Osterborg A; Hx-CD20-406 Study Investigators. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol* 2010; **28**: 1749-1755 [PMID: 20194866 DOI: 10.1200/JCO.2009.25.3187]

40 **Tobinai K**, Klein C, Oya N, Fingerle-Rowson G. A Review of Obinutuzumab (GA101), a Novel Type II Anti-CD20 Monoclonal Antibody, for the Treatment of Patients with B-Cell Malignancies. *Adv Ther* 2017; **34**: 324-356 [PMID: 28004361 DOI: 10.1007/s12325-016-0451-1]

41 **Goede V**, Klein C, Stilgenbauer S. Obinutuzumab (GA101) for the treatment of chronic lymphocytic leukemia and other B-cell non-hodgkin's lymphomas: a glycoengineered type II CD20 antibody. *Oncol Res Treat* 2015; **38**: 185-192 [PMID: 25877943 DOI: 10.1159/000381524]

42 **Goede V**, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, Chagorova T, de la Serna J, Dilhuydy MS, Illmer T, Opat S, Owen CJ, Samoylova O, Kreuzer KA, Stilgenbauer S, Döhner H, Langerak AW, Ritgen M, Kneba M, Asikanius E, Humphrey K, Wenger M, Hallek M. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014; **370**: 1101-1110 [PMID: 24401022 DOI: 10.1056/NEJMoa1313984]

43 **Goede V**, Fischer K, DyerM, Mülle L, Smolej L, Di Bernardo MC, Knapp A, Nielsen T, Hallek M. Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: final survival analysis of the CLL11 study. Abstract S151; 2018, 14-17 June, Stockholm, Sweden EHA Congress [Internet]. [cited 15 January 2021] Available from: <https://library.ehaweb.org/eha/2018/stockholm/215923/valentin.goede.overall.survival.benefit.of.obinutuzumab.over.rituximab.when.html?f=menu%3D14%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Aspeaker%3D664514>

44 **Marcus R**, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *N Engl J Med* 2017; **377**: 1331-1344 [PMID: 28976863 DOI: 10.1056/NEJMoa1614598]

45 **Cheson BD**, Chua N, Mayer J, Dueck G, Trněný M, Bouabdallah K, Fowler N, Delwail V, Press O, Salles G, Gribben JG, Lennard A, Lugtenburg PJ, Fingerle-Rowson G, Mattiello F, Knapp A, Sehn LH. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. *J Clin Oncol* 2018; **36**: 2259-2266 [PMID: 29584548 DOI: 10.1200/JCO.2017.76.3656]

46 **Vitolo U**, Trněný M, Belada D, Burke JM, Carella AM, Chua N, Abrisqueta P, Demeter J, Flinn I, Hong X, Kim WS, Pinto A, Shi YK, Tatsumi Y, Oestergaard MZ, Wenger M, Fingerle-Rowson G, Catalani O, Nielsen T, Martelli M, Sehn LH. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2017; **35**: 3529-3537 [PMID: 28796588 DOI: 10.1200/JCO.2017.73.3402]

47 **Jurczak W**, Zinzani PL, Gaidano G, Goy A, Provencio M, Nagy Z, Robak T, Maddocks K, Buske C, Ambarkhane S, Winderlich M, Dirnberger-Hertweck M, Korolkiewicz R, Blum KA. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Ann Oncol* 2018; **29**: 1266-1272 [PMID: 29444231 DOI: 10.1093/annonc/mdy056]

48 **Maddocks KJ**, Duell J, Gonzales Barca E, Jurczak W, Liberati AM, Nagy Z, Obr A, Gaidano G, André M, Kalakonda N, Dreyling MH, Zinzani PL, Dirnberger-Hertweck M, Weirather J, Ambarkhane SV, Salles GA. Update of the single-arm phase II L-MIND study of MOR208+lenalidomide(Len) in relapsed/refractory diffuse large B-cell lymphoma (R-R DLBCL): Response rates in patient subgroups with poor prognosis. *J Clin Oncol* 2019: **37**: 7521-7521 [DOI: 10.1200/JCO.2019.37.15\_suppl.7521]

49 **ClinicalTrials.gov**. A Trial to Evaluate the Efficacy and Safety of Tafasitamab With Bendamustine (BEN) Versus Rituximab (RTX) With BEN in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL) (B-MIND). [accessed January 20, 2021]. In: ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02763319> Clinicaltrials.gov Indentifier: NCT02763319

50 **ClinicalTrials.gov**. Phase Ib Study to Assess Safety and Preliminary Efficacy of Tafasitamab or Tafasitamab Plus Lenalidomide in Addition to R-CHOP in Patients With Newly Diagnosed DLBCL. [accessed January 21, 2021]. In: ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04134936> Clinicaltrials.gov Identifier: NCT04134936

51 **Logtenberg MEW**, Scheeren FA, Schumacher TN. The CD47-SIRPα Immune Checkpoint. *Immunity* 2020; **52**: 742-752 [PMID: 32433947 DOI: 10.1016/j.immuni.2020.04.011]

52 **Advani R**, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, Kline J, Roschewski M, LaCasce A, Collins GP, Tran T, Lynn J, Chen JY, Volkmer JP, Agoram B, Huang J, Majeti R, Weissman IL, Takimoto CH, Chao MP, Smith SM. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. *N Engl J Med* 2018; **379**: 1711-1721 [PMID: 30380386 DOI: 10.1056/NEJMoa1807315]

53 **Kim YH**, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, Whittaker S, Tokura Y, Vermeer M, Zinzani PL, Sokol L, Morris S, Kim EJ, Ortiz-Romero PL, Eradat H, Scarisbrick J, Tsianakas A, Elmets C, Dalle S, Fisher DC, Halwani A, Poligone B, Greer J, Fierro MT, Khot A, Moskowitz AJ, Musiek A, Shustov A, Pro B, Geskin LJ, Dwyer K, Moriya J, Leoni M, Humphrey JS, Hudgens S, Grebennik DO, Tobinai K, Duvic M; MAVORIC Investigators. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol* 2018; **19**: 1192-1204 [PMID: 30100375 DOI: 10.1016/S1470-2045(18)30379-6]

54 **Witzig TE**, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, Cripe L, Wiseman G, Olejnik T, Multani PS, White CA. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20**: 3262-3269 [PMID: 12149300 DOI: 10.1200/JCO.2002.11.017]

55 **Kaminski MS**, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, Regan D, Kison P, Fisher S, Kroll S, Wahl RL. 131I-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med* 2005; **352**: 441-449 [PMID: 15689582 DOI: 10.1056/NEJMoa041511]

56 **Popović L**, Jovanović D, Popović Ð. CD30 - the head of TNF-family… or a successful story of brentuximab vedotin. *Arch Oncol* 2013; **21**: 17-19 [doi: 10.2298/AOO1301017P]

57 **Younes A**, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, Forero-Torres A. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010; **363**: 1812-1821 [PMID: 21047225 DOI: 10.1056/NEJMoa1002965]

58 **Younes A**, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, Ramchandren R, Bartlett NL, Cheson BD, de Vos S, Forero-Torres A, Moskowitz CH, Connors JM, Engert A, Larsen EK, Kennedy DA, Sievers EL, Chen R. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; **30**: 2183-2189 [PMID: 22454421 DOI: 10.1200/JCO.2011.38.0410]

59 **Moskowitz CH**, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, Chen AI, Stiff P, Gianni AM, Carella A, Osmanov D, Bachanova V, Sweetenham J, Sureda A, Huebner D, Sievers EL, Chi A, Larsen EK, Hunder NN, Walewski J; AETHERA Study Group. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; **385**: 1853-1862 [PMID: 25796459 DOI: 10.1016/S0140-6736(15)60165-9]

60 **Moskowitz CH**, Walewski J, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, Chen AI, Stiff P, Viviani S, Bachanova V, Sureda A, McClendon T, Lee C, Lisano J, Sweetenham J. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood* 2018; **132**: 2639-2642 [PMID: 30266774 DOI: 10.1182/blood-2018-07-861641]

61 **Connors JM**, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, Younes A, Alekseev S, Illés Á, Picardi M, Lech-Maranda E, Oki Y, Feldman T, Smolewski P, Savage KJ, Bartlett NL, Walewski J, Chen R, Ramchandren R, Zinzani PL, Cunningham D, Rosta A, Josephson NC, Song E, Sachs J, Liu R, Jolin HA, Huebner D, Radford J; ECHELON-1 Study Group. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. *N Engl J Med* 2018; **378**: 331-344 [PMID: 29224502 DOI: 10.1056/NEJMoa1708984]

62 **Prince HM**, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, Zinzani PL, Wolter P, Sanches JA, Ortiz-Romero PL, Akilov OE, Geskin L, Trotman J, Taylor K, Dalle S, Weichenthal M, Walewski J, Fisher D, Dréno B, Stadler R, Feldman T, Kuzel TM, Wang Y, Palanca-Wessels MC, Zagadailov E, Trepicchio WL, Zhang W, Lin HM, Liu Y, Huebner D, Little M, Whittaker S, Duvic M; ALCANZA study group. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* 2017; **390**: 555-566 [PMID: 28600132 DOI: 10.1016/S0140-6736(17)31266-7]

63 **Pro B**, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, Matous J, Ramchandren R, Fanale M, Connors JM, Fenton K, Huebner D, Pinelli JM, Kennedy DA, Shustov A. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. *Blood* 2017; **130**: 2709-2717 [PMID: 28974506 DOI: 10.1182/blood-2017-05-780049]

64 **Horwitz S**, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, Bartlett NL, Christensen JH, Morschhauser F, Domingo-Domenech E, Rossi G, Kim WS, Feldman T, Lennard A, Belada D, Illés Á, Tobinai K, Tsukasaki K, Yeh SP, Shustov A, Hüttmann A, Savage KJ, Yuen S, Iyer S, Zinzani PL, Hua Z, Little M, Rao S, Woolery J, Manley T, Trümper L; ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet* 2019; **393**: 229-240 [PMID: 30522922 DOI: 10.1016/S0140-6736(18)32984-2]

65 **Sehn LH**, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, Assouline S, Kim TM, Kim WS, Ozcan M, Hirata J, Penuel E, Paulson JN, Cheng J, Ku G, Matasar MJ. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2020; **38**: 155-165 [PMID: 31693429 DOI: 10.1200/JCO.19.00172]

66 **ClinicalTrials.gov**. A Study of Obinutuzumab, Rituximab, Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory Follicular Lymphoma (FL) or Diffuse Large B-Cell Lymphoma (DLBCL). [accessed January 30, 2021]. In ClinicalTrials.gov [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT02611323 ClinicalTrials.gov Identifier: NCT02611323

67 **ClinicalTrials.gov**. A Study Comparing the Efficacy and Safety of Polatuzumab Vedotin With Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) Versus Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Participants With Diffuse Large B-Cell Lymphoma (POLARIX). [accessed 2021 Feb 2]. In ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03274492> ClinicalTrials.gov Identifier: NCT03274492

68 **Kreitman RJ**, Dearden C, Zinzani PL, Delgado J, Karlin L, Robak T, Gladstone DE, le Coutre P, Dietrich S, Gotic M, Larratt L, Offner F, Schiller G, Swords R, Bacon L, Bocchia M, Bouabdallah K, Breems DA, Cortelezzi A, Dinner S, Doubek M, Gjertsen BT, Gobbi M, Hellmann A, Lepretre S, Maloisel F, Ravandi F, Rousselot P, Rummel M, Siddiqi T, Tadmor T, Troussard X, Yi CA, Saglio G, Roboz GJ, Balic K, Standifer N, He P, Marshall S, Wilson W, Pastan I, Yao NS, Giles F. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. *Leukemia* 2018; **32**: 1768-1777 [PMID: 30030507 DOI: 10.1038/s41375-018-0210-1]

69 **Kantarjian H**, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foà R, Bassan R, Arslan Ö, Sanz MA, Bergeron J, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Brüggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med* 2017; **376**: 836-847 [PMID: 28249141 DOI: 10.1056/NEJMoa1609783]

70 **Przepiorka D**, Ko CW, Deisseroth A, Yancey CL, Candau-Chacon R, Chiu HJ, Gehrke BJ, Gomez-Broughton C, Kane RC, Kirshner S, Mehrotra N, Ricks TK, Schmiel D, Song P, Zhao P, Zhou Q, Farrell AT, Pazdur R. FDA Approval: Blinatumomab. *Clin Cancer Res* 2015; **21**: 4035-4039 [PMID: 26374073 DOI: 10.1158/1078-0432.CCR-15-0612]

71 **Dufner V**, Sayehli CM, Chatterjee M, Hummel HD, Gelbrich G, Bargou RC, Goebeler ME. Long-term outcome of patients with relapsed/refractory B-cell non-Hodgkin lymphoma treated with blinatumomab. *Blood Adv* 2019; **3**: 2491-2498 [PMID: 31451445 DOI: 10.1182/bloodadvances.2019000025]

72 **Schuster SJ**, Bartlett NL, Assouline S, Yoon SS, Bosch F, Sehn LH, Cheah C, Shadman M, Gregory GP, Ku M, Wei MC, Yin S, Kwan A, Yousefi K, Hernandez G, Li CC, O'Hear C, Budde LE. Mosunetuzumab Induces Complete Remissions in Poor Prognosis Non-Hodgkin Lymphoma Patients, Including Those Who Are Resistant to or Relapsing After Chimeric Antigen Receptor T-Cell (CAR-T) Therapies, and Is Active in Treatment through Multiple Lines. *Blood* 2019; **134**: 6 [doi: 10.1182/blood-2019-123742]

73 **Dickinson MJ,** Morschhauser F, Iacoboni G, Carlo-Stella C, Offner FC, Sureda A, Salles G, Martinez-Lopez J, Crump M, Lundberg L, Dixon M, Kwan A, Wei MC, Bröske AM, Carlile D, O'Hear C, Hutchings M. CD20-TCB in relapsed or refractory non-hodgkin lymphoma: durable complete responses and manageable safety observed at clinically relevant doses in phase i dose escalation EHA Meeting 2020; S241 [cited 3 January 2021] Available from: https://library.ehaweb.org/eha/2020/eha25th/293690/michael.j.dickinson.cd20-tcb.in.relapsed.or.refractory.non-hodgkin.lymphoma.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D1%2Amedia%3D1

74 **Bannerji R**, Allan JN, Arnason JE, Brown JR, Advani RH, Barnes JA, Ansell S, O'Brien S, Chavez J, Duell J, David K, Martin P, Joyce R, Charnas R, Ambati S, Adriaens L, Ufkin M, Zhu M, Li J, Gasparini P, Ibrahim A, Jankovic V, Fiaschi N, Aina O, Zhang W, Deering R, Hamon S, Thurston G, Murphy A, Weinreich D, Yancopoulos G, Lowy I, Sternberg D, Topp MS. Clinical Activity of REGN1979, a Bispecific Human, Anti-CD20 x Anti-CD3 Antibody, in Patients with Relapsed/Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL). *Blood* 2019; **134**: 762 [doi: 10.1182/blood-2019-122451]

75 **Morschhauser F**, Carlo-Stella C, Offner F, Salles G, Hutchings M, Iacoboni G, Sureda A, Crump M, Martinez-Lopez J, Thomas D, Morcos P, Ferlini C, Keelara A, Bröske AM, Bacac M, Dimier N, Moore T, Weisser M, Dickinson M. Dual CD20-Targeted Therapy With Concurrent CD20-TCB and Obinutuzumab Shows Highly Promising Clinical Activity and Manageable Safety in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma: Preliminary Results From a Phase Ib Trial. *Blood* 2019; **134**: 1584 [doi: 10.1182/blood-2019-123949]

76 **Robert C**, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; **372**: 2521-2532 [PMID: 25891173 DOI: 10.1056/NEJMoa1503093]

77 **Larkin J**, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015; **373**: 23-34 [PMID: 26027431 DOI: 10.1056/NEJMoa1504030]

78 **Reck M**, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016; **375**: 1823-1833 [PMID: 27718847 DOI: 10.1056/NEJMoa1606774]

79 **Socinski MA**, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley G, Kelsch C, Lee A, Coleman S, Deng Y, Shen Y, Kowanetz M, Lopez-Chavez A, Sandler A, Reck M; IMpower150 Study Group. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* 2018; **378**: 2288-2301 [PMID: 29863955 DOI: 10.1056/NEJMoa1716948]

80 **Motzer RJ**, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, Venugopal B, Kollmannsberger C, Negrier S, Uemura M, Lee JL, Vasiliev A, Miller WH Jr, Gurney H, Schmidinger M, Larkin J, Atkins MB, Bedke J, Alekseev B, Wang J, Mariani M, Robbins PB, Chudnovsky A, Fowst C, Hariharan S, Huang B, di Pietro A, Choueiri TK. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* 2019; **380**: 1103-1115 [PMID: 30779531 DOI: 10.1056/NEJMoa1816047]

81 **Bellmunt J**, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF, Bajorin DF; KEYNOTE-045 Investigators. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med* 2017; **376**: 1015-1026 [PMID: 28212060 DOI: 10.1056/NEJMoa1613683]

82 **Schmid P**, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med* 2020; **382**: 810-821 [PMID: 32101663 DOI: 10.1056/NEJMoa1910549]

83 **Schmid P**, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im SA, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S, Emens LA; IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* 2018; **379**: 2108-2121 [PMID: 30345906 DOI: 10.1056/NEJMoa1809615]

84 **Armand P**, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, Timmerman JM, Collins GP, Ramchandren R, Cohen JB, De Boer JP, Kuruvilla J, Savage KJ, Trneny M, Shipp MA, Kato K, Sumbul A, Farsaci B, Ansell SM. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. *J Clin Oncol* 2018; **36**: 1428-1439 [PMID: 29584546 DOI: 10.1200/JCO.2017.76.0793]

85 **Chen R**, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, Radford J, Ribrag V, Molin D, Vassilakopoulos TP, Tomita A, von Tresckow B, Shipp MA, Zhang Y, Ricart AD, Balakumaran A, Moskowitz CH; KEYNOTE-087. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. *J Clin Oncol* 2017; **35**: 2125-2132 [PMID: 28441111 DOI: 10.1200/JCO.2016.72.1316]

86 **Kuruvilla J**, Ramchandren R, Santoro A, Paszkiewicz-Kozik E, Gasiorowski R, Johnson N, Melnichenko V, Fogliatto LM, Goncalves I, Oliveira J, Buccheri V, Perini GF, Goldschmidt N, Alekseev S, Kryachok I, Sekiguchi N, Zhu Y, Nahar A, Marinello P, Zinzani PL. KEYNOTE-204: Randomized, open-label, phase III study of pembrolizumab (pembro) vs brentuximab vedotin (BV) in relapsed or refractory classic Hodgkin lymphoma (R/R cHL). *J Clin Oncol* 2020 **38**: 8005-8005 [DOI: 10.1200/JCO.2020.38.15\_suppl.8005]

87 **ClinicalTrials.gov**. Immunotherapy (Nivolumab or Brentuximab-Vedotin) Plus Combination Chemotherapy in Treating Patients With Newly Diagnosed Stage III-IV Classic Hodgkin Lymphoma. [accessed 2021 Jan 22]. In: ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03907448> ClinicalTrials.gov Identifier: NCT 03907448

88 **Herrera AF**, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, LaCasce AS, Ansell SM, Moskowitz CH, Fenton K, Ogden CA, Taft D, Zhang Q, Kato K, Campbell M, Advani RH. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 2018; **131**: 1183-1194 [PMID: 29229594 DOI: 10.1182/blood-2017-10-811224]

89 **Diefenbach CS**, Hong F, Ambinder RF, Cohen JB, Robertson MJ, David KA, Advani RH, Fenske TS, Barta SK, Palmisiano ND, Svoboda J, Morgan DS, Karmali R, Sharon E, Streicher H, Kahl BS, Ansell SM. Ipilimumab, nivolumab, and brentuximab vedotin combination therapies in patients with relapsed or refractory Hodgkin lymphoma: phase 1 results of an open-label, multicentre, phase 1/2 trial. *Lancet Haematol* 2020; **7**: e660-e670 [PMID: 32853585 DOI: 10.1016/S2352-3026(20)30221-0]

90 **Twa DD**, Chan FC, Ben-Neriah S, Woolcock BW, Mottok A, Tan KL, Slack GW, Gunawardana J, Lim RS, McPherson AW, Kridel R, Telenius A, Scott DW, Savage KJ, Shah SP, Gascoyne RD, Steidl C. Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. *Blood* 2014; **123**: 2062-2065 [PMID: 24497532 DOI: 10.1182/blood-2013-10-535443]

91 **Armand P**, Rodig S, Melnichenko V, Thieblemont C, Bouabdallah K, Tumyan G, Özcan M, Portino S, Fogliatto L, Caballero MD, Walewski J, Gulbas Z, Ribrag V, Christian B, Perini GF, Salles G, Svoboda J, Zain J, Patel S, Chen PH, Ligon AH, Ouyang J, Neuberg D, Redd R, Chatterjee A, Balakumaran A, Orlowski R, Shipp M, Zinzani PL. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. *J Clin Oncol* 2019; **37**: 3291-3299 [PMID: 31609651 DOI: 10.1200/JCO.19.01389]

92 **Khodadoust MS**, Rook AH, Porcu P, Foss F, Moskowitz AJ, Shustov A, Shanbhag S, Sokol L, Fling SP, Ramchurren N, Pierce R, Davis A, Shine R, Li S, Fong S, Kim J, Yang Y, Blumenschein WM, Yearley JH, Das B, Patidar R, Datta V, Cantu E, McCutcheon JN, Karlovich C, Williams PM, Subrahmanyam PB, Maecker HT, Horwitz SM, Sharon E, Kohrt HE, Cheever MA, Kim YH. Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sézary Syndrome: A Multicenter Phase II Study. *J Clin Oncol* 2020; **38**: 20-28 [PMID: 31532724 DOI: 10.1200/JCO.19.01056]

93 **June CH**, Maus MV, Plesa G, Johnson LA, Zhao Y, Levine BL, Grupp SA, Porter DL. Engineered T cells for cancer therapy. *Cancer Immunol Immunother* 2014; **63**: 969-975 [PMID: 24943274 DOI: 10.1007/s00262-014-1568-1]

94 **Brudno JN**, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. *Blood Rev* 2019; **34**: 45-55 [PMID: 30528964 DOI: 10.1016/j.blre.2018.11.002]

95 **Crump M**, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017; **130**: 1800-1808 [PMID: 28774879 DOI: 10.1182/blood-2017-03-769620]

96 **Neelapu SS**, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Timmerman JM, Stiff PJ, Friedberg JW, Flinn IW, Goy A, Hill BT, Smith MR, Deol A, Farooq U, McSweeney P, Munoz J, Avivi I, Castro JE, Westin JR, Chavez JC, Ghobadi A, Komanduri KV, Levy R, Jacobsen ED, Witzig TE, Reagan P, Bot A, Rossi J, Navale L, Jiang Y, Aycock J, Elias M, Chang D, Wiezorek J, Go WY. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017; **377**: 2531-2544 [PMID: 29226797 DOI: 10.1056/NEJMoa1707447]

97 **Schuster SJ**, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I, Bachanova V, Foley SR, Ho PJ, Mielke S, Magenau JM, Holte H, Pantano S, Pacaud LB, Awasthi R, Chu J, Anak Ö, Salles G, Maziarz RT; JULIET Investigators. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med* 2019; **380**: 45-56 [PMID: 30501490 DOI: 10.1056/NEJMoa1804980]

98 **Abramson JS**, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, Mehta A, Purev E, Maloney DG, Andreadis C, Sehgal A, Solomon SR, Ghosh N, Albertson TM, Garcia J, Kostic A, Mallaney M, Ogasawara K, Newhall K, Kim Y, Li D, Siddiqi T. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet* 2020; **396**: 839-852 [PMID: 32888407 DOI: 10.1016/S0140-6736(20)31366-0]

99 **Wang M**, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, Timmerman JM, Holmes H, Jaglowski S, Flinn IW, McSweeney PA, Miklos DB, Pagel JM, Kersten MJ, Milpied N, Fung H, Topp MS, Houot R, Beitinjaneh A, Peng W, Zheng L, Rossi JM, Jain RK, Rao AV, Reagan PM. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med* 2020; **382**: 1331-1342 [PMID: 32242358 DOI: 10.1056/NEJMoa1914347]

100 **Porter DL**, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, Bagg A, Marcucci KT, Shen A, Gonzalez V, Ambrose D, Grupp SA, Chew A, Zheng Z, Milone MC, Levine BL, Melenhorst JJ, June CH. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med* 2015; **7**: 303ra139 [PMID: 26333935 DOI: 10.1126/scitranslmed.aac5415]

101 **Siddiqi T**, Soumerai J, Dorritie K, Stephens D, Riedell P, Arnason J, Kipps T, Gillenwater H, Gong L, Dubovsky J, Rytlewski J, Yang L, Wierda W. Rapid Undetectable MRD (uMRD) Responses in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treated with Lisocabtagene Maraleucel (liso-cel), a CD19-Directed CAR T Cell Product: Updated Results from Transcend CLL 004, a Phase 1/2 Study Including Patients with High-Risk Disease Previously Treated with Ibrutinib. *Blood* 2019; **134**: 503 [DOI: 10.1182/blood-2019-127603]

102 **Jacobson C**, Chavez J, Sehgal A, William B, Munoz J, Salles G, Casulo C, Munshi P, Maloney D, Vos S, Reshef R, Leslie L, Yakoub-Agha I, Oluwole O, Fung H, PlaksV, Yang Y, Lee J, Avanzi M, Neelapu SS. Interim analysis of ZUMA-5: A phase II study of axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory indolent non-Hodgkin lymphoma (R/R iNHL). *J Clin Oncol* 2020 **38**: 8008-8008 [DOI: 10.1200/JCO.2020.38.15\_suppl.8008]

103 **Bollard CM**, Gottschalk S, Torrano V, Diouf O, Ku S, Hazrat Y, Carrum G, Ramos C, Fayad L, Shpall EJ, Pro B, Liu H, Wu MF, Lee D, Sheehan AM, Zu Y, Gee AP, Brenner MK, Heslop HE, Rooney CM. Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. *J Clin Oncol* 2014; **32**: 798-808 [PMID: 24344220 DOI: 10.1200/JCO.2013.51.5304]

104 **Prockop S**, Doubrovina E, Suser S, Heller G, Barker J, Dahi P, Perales MA, Papadopoulos E, Sauter C, Castro-Malaspina H, Boulad F, Curran KJ, Giralt S, Gyurkocza B, Hsu KC, Jakubowski A, Hanash AM, Kernan NA, Kobos R, Koehne G, Landau H, Ponce D, Spitzer B, Young JW, Behr G, Dunphy M, Haque S, Teruya-Feldstein J, Arcila M, Moung C, Hsu S, Hasan A, O'Reilly RJ. Off-the-shelf EBV-specific T cell immunotherapy for rituximab-refractory EBV-associated lymphoma following transplantation. *J Clin Invest* 2020; **130**: 733-747 [PMID: 31689242 DOI: 10.1172/JCI121127]

105 **Nastoupil LJ**, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, Dahiya S, Lunning M, Lekakis L, Reagan P, Oluwole O, McGuirk J, Deol A, Sehgal AR, Goy A, Hill BT, Vu K, Andreadis C, Munoz J, Westin J, Chavez JC, Cashen A, Bennani NN, Rapoport AP, Vose JM, Miklos DB, Neelapu SS, Locke FL. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. *J Clin Oncol* 2020; **38**: 3119-3128 [PMID: 32401634 DOI: 10.1200/JCO.19.02104]

106 **Lee DW**, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, Maus MV, Park JH, Mead E, Pavletic S, Go WY, Eldjerou L, Gardner RA, Frey N, Curran KJ, Peggs K, Pasquini M, DiPersio JF, van den Brink MRM, Komanduri KV, Grupp SA, Neelapu SS. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019; **25**: 625-638 [PMID: 30592986 DOI: 10.1016/j.bbmt.2018.12.758]

107 **Brudno JN**, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood* 2016; **127**: 3321-3330 [PMID: 27207799 DOI: 10.1182/blood-2016-04-703751]

108 **Rouce RH**. The earlier the better: timely mitigation of CRS. *Blood* 2019; **134**: 2119-2120 [PMID: 31830277 DOI: 10.1182/blood.2019003618]

109 **Gardner RA**, Ceppi F, Rivers J, Annesley C, Summers C, Taraseviciute A, Gust J, Leger KJ, Tarlock K, Cooper TM, Finney OC, Brakke H, Li DH, Park JR, Jensen MC. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. *Blood* 2019; **134**: 2149-2158 [PMID: 31697826 DOI: 10.1182/blood.2019001463]

110 **Popovic M,** Matovina-Brko G, Petrovic D, Vranjkovic B, Radic J, Popovic L. Prognostic value of Age-Adjusted International Prognostic Index in patients with relapsed or refractory Diffuse Large B-Cell Lymphoma- a single centre experience. *Med Pregl* 2019; **72**: 25-29 [DOI: 10.2298/MPNS1902025P]

111 **ClinicalTrials.gov**. Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7). [accessed January 23, 2021]. In: ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03391466> ClinicalTrials.gov Identifier: NCT03391466

112 **ClinicalTrials.gov**. Tisagenlecleucel in Adult Patients With Aggressive B-cell Non-Hodgkin Lymphoma (BELINDA). [accessed January 10, 2021]. In: ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03570892> ClinicalTrials.gov Identifier: NCT03570892

113 **ClinicalTrials.gov**. A Study to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects With High-risk, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM). [accessed January 24, 2021]. In: ClinicalTrials.gov [Internet]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03575351> ClinicalTrials.gov Identifier: NCT03575351

**Footnotes**

**Conflict-of-interest statement:** The authors have no competing interests to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding Author's Membership in Professional Societies:** European Society for Medical Oncology, No. 331412

**Peer-review started:** February 13, 2021

**First decision:** March 17, 2021

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** Serbia

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Li SC **S-Editor:** Gong ZM **L-Editor:** Filipodia **P-Editor:**

**Table 1 Monoclonal antibody studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug (Ref.)** | **Target** | **No. of patients** | **Study design** | **Study phase** | **Results** |
| Obinutuzumab | CD20 |  |  |  |  |
| [42] |  | 781 | CLL (CIRS ≥ 6) O + Clb *vs* R + Clb | 3 | PFS: 28.9 mo *vs* 15.7 mo (HR 0.49, *P* < 0.0001; OS: NR *vs* 73.1 mo (HR 0.76, *P* = 0.0245) Grade ≥ 3 AEs: Infusion reactions 20% *vs* 4%, Neutropenia 33% *vs* 28% |
| [44] |  | 1202 | FL (untreated) O + Chemo *vs* R + Chemo | 3 | 3-yr PFS rate: 80.0% *vs* 73.3% HR 0.66 *P* = 0.001 ORR: 88.5% *vs* 86.9% 3-yr OS rate: 94.0% *vs* 92.1% (HR 0.75, *P* = 0.21) Grade ≥ 3 AEs: 74.6% *vs* 67.8% |
| [45] |  | 413 | FL (rituximab refractory) O + Benda *vs* Benda | 3 | PFS: NR *vs* 14.9 mo (HR 0.55, *P* = 0.0001) OS: ND Grade ≥ 3 AEs: Neutropenia 33% *vs* 26%; Infusion reactions 11% *vs* 6% |
| Tafasitamab[47] | CD19 | 92 | DLBCL R/RT + Lenalidomide | 2 | ORR: 43% CR: 18% PFS: 12.1 mo Grade ≥ 3 AEs: Neutropenia 48%, Thrombocytopenia 17%, Febrile neutropenia 12% |
| Magrolimab[52] | CD47 | 22 | R/R DLBCL or FL M + R | 1b | DLBCL ORR/CR: 40%/33% FL ORR/CR: 71%/43% AEs: Anemia, Infusion reactions |
| Mogamulizumab[53] | CCR4 | 372 | CTCL R/R Mo *vs* Vorinostat | 3 | PFS: 7.7 mo *vs* 3.1 mo (HR 0.53, *P* < 0.0001) Grade ≥ 3 AEs: Mo: pyrexia 4%, cellulitis 3%; V: cellulitis 3%, PE 3%, sepsis 3% |

AE: adverse event; Benda: Bendamustin; CCR4: C chemokine receptor 4; Chemo: chemotherapy; CIRS: cumulative illness rating scale; Clb: Chlorambucil; CLL: chronic lymphocytic leukemia; CR: complete response; CTCL: cutaneous T-cell lymphomas; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; M: Macrolimab; Мо: Mogalizumab; NR: not reached; O: obinutuzumab; ORR: objective response rate; OS: overall survival; PE: pulmonary embolism. PFS: progression-free survival; R: Rituximab; R/R: relapsed/refractory; V: Vorinostat.

**Table 2 Antibody-drug conjugate studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug [Ref.]** | **Target** | **No. of patients** | **Study design** | **Study phase** | **Results** |
| Brentuximab-vedotin | CD30 |  |  |  |  |
| [10,58] |  | 102 | R/R cHL  | 2 | ORR/CR: 72%/33% PFS 9.3 mo; OS 40.5 mo; AEs: PSN 42%, nausea 35%, fatigue 34% |
| [59,60] |  | 329 | R/R high-risk cHL maint BV *vs* Pbo | 3 | 5-yr PFS rate 59% *vs* 41% (HR 0.52) OS: NR AEs: PSN (90% resolved) |
| [61] |  | 1334 | Untreated cHL CS III/IV BV + AVD *vs* ABVD | 3 | 2-yr mPFS rate: 82.1% *vs* 77.2% (HR 0.77, *P* = 0.04) AEs: Neutropenia 58% *vs* 45%, PSN 67% *vs* 43%, PN 1% *vs* 3% |
| [62] |  | 131 | R/R CTCL or cALCL; *vs* MTX or BV | 3 | ORR4: 56.3% *vs* 12.5% (*P* < 0.0001); EFS: 9.4 mo *vs* 2.3 mo (HR 0.28, *P* < 0.0001) Grade ≥ 3 AEs: 41% *vs* 47%; PSN: 67% *vs* 6% |
| [63] |  | 58 | R/R ALCL | 2 | ORR/CR: 86%/66%; 5-yr OS rate: 60%, 5-yr OS rate (in CR *vs* non-CR): 79% *vs* 25% |
| [64] |  | 601 | Untreated CD30+ sALCL; BV + CHP *vs* CHOP | 3 | PFS: 48.2 mo *vs* 20.8 mo (HR 0.71, *P* = 0.011); OS: NR *vs* NR (HR 0.66, *P* = 0.024) AEs: febrile neutropenia 18% *vs* 15%, PSN 52% *vs* 55% |
| Polatuzumab vedotin[65] | CD79b | 80 | R/R DLBCL; PV + R + Benda *vs* R + Benda | 2 | CR: 40% *vs* 17.5% PFS: 9.5 mo *vs* 3.7 mo (HR 0.63, *P* < 0.001) Grade ≥ 3 AEs: Anemia 28.2% *vs* 17.9%, Neutropenia 46.2% *vs* 33.3% Thrombocytopenia 41.0% *vs* 23.1% |
| Moxetumomab-pasudotox[68] | CD22 | 80 | R/R HCL | 2 | ORR: 75% CR: 30% (85% MRD-); AEs: Edema 39%, nausea 35%, fatigue 34%, headache 33% |

ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine; AE: adverse event; AE: adverse event; ALCL: anaplastic large-cell lymphoma; AVD: doxorubicin, bleomycin, vinblastine, dacarbazine; Benda: Bendamustin; BV: Brentuximab vedotin; cHL: classic Hodgkin lymphoma; CHOP: cyclophosphamide, adriamycin, oncovin, prednisone; CHP: cyclophosphamide, adriamycin, prednisone; CR: complete response; CS: clinical stage; CTCL: cutaneous large-cell lymphoma; DLBCL: diffuse large b-cell lymphoma; EFS: event-free survival; HCL: hairy cell leukemia; maint: maintenance; MRD: minimal residual disease. MTX: Methotrexate; NR: not reached; ORR: objective response rate; OS: Overall survival; Pbo: Placebo; PFS: progression-free survival; PNS: peripheral neuropathy syndrome; PV: Polatuzumab vedotin; R: Rituximab; R/R: relapsed/refractory.

**Table 3 Bispecific antibody studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug** | **Target** | **No. of patients** | **Study design** | **Study phase** | **Results** |
| Blinatumomab[71] | CD3/CD19 | 38 | R/R FL, MCL, DLBCL | 1 | ORR/CR: 64%/38%; PFS 6.7 mo; OS 4.6 yr; OS ( for CR/PR): 7.7 yr; AEs: Infections (pneumonia, diarrhea, sepsis) |
| Mosunetuzumab[72] | CD3/CD20 | 218 | R/R B-NHL | 1 | NHL ORR/CR: 64.1%/42.2%; DLBCL ORR/CR: 34.7%/16.6% AEs: CRS 28.4%, NAEs: 44% |
| CD20-TCB[73] | CD3/CD20 | 38 | R/R DLBCL | 1 | ORR/CR: 47%/34% AEs: CRS 55.1%, Neutropenia 34.7% |

AE: adverse event; CR: complete response; CRS: cytokine releasing syndrome; DLBCL: diffuse large B-Cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; NHL: non-Hodgkin lymphoma; ORR: objective response rate; OS: Overall survival; PFS: progression-free survival; R/R: relapsed/refractory.

**Table 4 Checkpoint inhibitor studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug [Ref.]** | **Target** | **No. of patients** | **Study design** | **Study phase** | **Results** |
| Nivolumab | PD-1 |  |  |  |  |
| [84] |  | 243 | R/R cHL (after ASCT) | 2 | ORR/CR: 69%/40%; PFS: 14.7 mo, Grade ≥ 3 AEs: lipase increases 5%, neutropenia 3%, ALT increases 3% |
| [88] |  | 61 | R/R cHL with BV | 1/2 | ORR/CR: 82%/61%; AEs: Infusion reactions 44% (BV), corticosteroid therapy 8% |
| [89] |  | 64 | R/R cHL Nivo + BV, Ipi + BV, Nivo + Ipi + BV | 1/2 | ORR: 89%, 76%, 82% Grade ≥ 3 AEs: 16%, 42%, 50% |
| Pembrolizumab | PD-1 |  |  |  |  |
|  [85] |  | 210 | R/R cHL | 2 | ORR/CR: 69%/22.4% 6-mos DoR rate: 75.6% TRAEs: hypothyroidism 12.4%, pyrexia 10.5% |
| [86] |  | 304 | R/R cHL *vs* BV | 3 | PFS: 13.2 mo *vs* 8.3 mo (HR 0.65, *P* = 0.00271), ORR/CR: 65.6%/24.5% *vs* 54.2%/24.2% TRAEs: 19.6% *vs* 25%  |
| [91] |  | 74 | R/R PMBCL | 2 | ORR/CR: 45%/13% DoR: NR (12.5 mo FU); Grade ≥ 3 TRAEs: 23% |
| [92] |  | 24 | R/R CTCL | 2 | ORR: 38%; IRAEs: 17% |

AE: adverse event; ALT: alanine amino transferase; ASCT: autologous stem cell transplantation; BV: brentuximab vedotin; cHL: classic Hodgkin lymphoma; CR: complete response; CTCL: Cutaneous T-cell lymphoma; DoR: duration of response; Ipi: Ipilimumab; IRAEs: immune related adverse event; Nivo: Nivolumab; NR: not reached. ORR: objective response rate; PFS: progression-free survival; PMBCL: primary mediastinal B-cell lymphoma; R/R: relapsed/refractory; TRAEs: treatment-related adverse event.

**Table 5 Chimeric antigen receptor T cell studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug [Ref.]** | **Target/co-stimulator** | **No. of patients** | **Study design** | **Study phase** | **Results** |
| Axicabtagene-ciloleucel[96] | CD19/CD28 | 111 | R/R DLBCL  | 2 | ORR/CR: 82%/54%; DoR (FU 15.4 mo): 42%, 40% CR; 18-mos OS rate: 52% Grade ≥ 3 AEs: neutropenia 78%, CRS 13%, ICANS 28%  |
| Tisagenlecleucel[97] | CD19/4-1BB | 93 | R/R DLBCL | 2 | ORR/CR: 52%/40%; DoR (FU 12 mo): 65%, 79% CR; Grade ≥ 3 AEs: CRS 22%, ICANS 12%, cytopenias 28%, infections 20% |
| Lisocabtagene-maraleucel[98] | CD19/4-1BB | 344 | R/R DLBCL | 2 | ORR/CR: 73%/53%; Grade ≥ 3 AEs: CRS 2%, ICANS 10% |
| Brexucabtagene-autoleucel (KTE-X19)[99] | CD19/CD28 | 74 | R/R MCL | 2 | ORR/CR: 93%/67%; 1-yr PFS/ OS rate: 61%/83%; Grade ≥ 3 AEs: cytopenias 94%, infections 32%, CRS 15%, ICANS 31% |
| Tisagenlecleucel[100] | CD19/4-1BB | 14 | R/R CLL | 1 | ORR/CR: 57%/28%; No relapses in CR patients (*n* = 4). All CR patients developed CRS |
| Lisocabtagene-maraleucel[101] | CD19/4-1BB | 23 | R/R CLL (56.5% progressed after ibrutinib and venetoclax) | 1/2 | ORR/CR: 82%/45.5%; Grade ≥ 3 AEs: anemia 96%, thrombocytopenia 70%, CRS 9%, ICANS 22% |
| Axicabtagene-ciloleucel[102] | CD19/CD28 | 94 | R/R FL, MZL | 2 | ORR/CR: FL 95%/80% MZL 86%/71%; Grade ≥ 3 AEs: neutropenia 33%, anemia 28%, CRS 11%, ICANS 19% |

AE: adverse event; CLL: chronic lymphocytic leukemia; CR: complete response; CRS: cytokine releasing syndrome; DLBCL: diffuse large B-cell lymphoma; DoR: duration of response; FL: follicular lymphoma. FU: follow-up; ICANS: Immune effector cell-associated neurotoxicity syndrome; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; ORR: objective response; OS: overall survival; PFS: Progression-free survival; R/R: relapsed/refractory.