Seminars in Immunopathology (2019) 41:111–124
https://doi.org/10.1007/s00281-018-0696-7

REVIEW

Cancer immune therapy for lymphoid malignancies: recent advances

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Received: 12 June 2018 / Accepted: 14 June 2018 / Published online: 13 July 2018

Abstract

Immunotherapy has played an important part in improving the life of patients with lymphoproliferative diseases especially since the addition of rituximab to chemotherapy in the CD20-positive neoplasms in the 1990s. While this field of passive immunotherapy is continuously evolving, several breakthroughs will expand the treatment modalities to include more active immunotherapy. With the approval of immune checkpoint-blocking antibodies for Hodgkin lymphoma and bispecific antibodies for acute lymphoblastic leukemia (ALL), activation of endogenous T cells already plays a role in several lymphoid malignancies. With the approval of cellular therapies with CAR-T cells for ALL and diffuse large B cell lymphoma, the impact of the manipulation of immune responses is taken even further. Vaccines are cellular therapies in the opposite end of the spectrum in terms of side effects, and while the big breakthrough is still to come, the prospect of a very low-toxic immunotherapy which could be applicable also in premalignant states or in frail patients drives a considerable research activity in the area. In this review, we summarize the mechanisms of action and clinical data on trials in the lymphoid neoplasms with chimeric antigen receptor T cells, bispecific antibodies, immune checkpoint-blocking antibodies, and antineoplastic vaccination therapy.

Keywords Immunotherapy · Lymphoma · Leukemia · Multiple myeloma · CAR-T cells · Bispecific antibodies · Vaccination therapy · Immune checkpoint inhibitors

Introduction

Lymphoproliferative neoplasms are a large group of heterogeneous malignancies arising from different stages of lymphocyte maturity and ranging from immature lymphoblasts in acute lymphoblastic leukemias (ALLs) to final differentiated plasma cells in multiple myeloma (MM). During lymphocyte development, the lymphocytes gain highly specialized functions and can be discerned by distinct surface markers, which have been attractive for targeted therapy.

Lymphoproliferative neoplasms remain difficult diseases to control. Modulating the immune system is an attractive treatment option, as the immune system is capable of attacking leukemic cells. The best evidence for the potential effect of immunotherapy against leukemia was in many years the often sustained remissions associated with hematopoietic stem cell transplantation (HSCT) in hematological malignancies. Although initially considered a method of bone marrow rescue after high-dose chemotherapy, it is now well known that HSCT generates a graft-versus-leukemia response, which can be further enhanced with donor lymphocyte infusion. HSCT is still the chosen therapeutic option for most hematologic malignancies, even though it remains a dangerous procedure with many complications. Thus, cancer immunologists have sought additional approaches to stimulate anti-leukemia immunity in order to activate the adoptive immune system, and recent years have given us several major breakthroughs. In this review, we focus on giving a condensed overview of the

This article is a contribution to the special issue on Anti-cancer Immunotherapy: Breakthroughs and Future Strategies – Guest Editor: Mads Hald Andersen

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00281-018-0696-7) contains supplementary material, which is available to authorized users.

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progress in immunotherapy for lymphoproliferative neoplasms. This includes the immune treatment modalities of chimeric antigen receptor (CAR) T cells, immune checkpoint-blocking antibodies, bispecific antibodies, and vaccination therapy. The evolving field of monoclonal antibody (mAb) therapy is elaborate and beyond the scope of this review. In addition, the clinical and pathological distinctions between lymphoproliferative neoplasms will not be covered. The clinical data from selected studies will be summarized for ALL and CLL in Table 1, for lymphomas in Table 2, and multiple myeloma in Table 3.

Chimeric antigen receptor T cells

CAR-T cells are T cells genetically modified to express a CAR. This receptor consists of a variable immunoglobulin chain coupled with a T cell receptor (TCR) CD3 signaling domain (Fig. 1(D)). A costimulatory domain, either CD28 or 4-1BB, has been added to second-generation CARs and both are present on third-generation CARs. Modern gene editing techniques, such as CRISPR-Cas9, are used for further interesting developments. The variable immunoglobulin chain is responsible for antigen recognition, and the most successful target has been CD19 [38]. CAR-T cell therapy has an inherent risk of cytokine release syndrome (CRS), characterized by shock-related symptoms due to the release of cytokines such as IL-6 when the T cells are infused and activated simultaneously. Despite being a severe and potentially life-threatening side effect, CRS is well managed using the anti-IL6R mAb tocilizumab and steroids. Neurotoxicity is another potentially severe side effect with clinical presentation overlapping CRS, but seems to have a different pathogenesis. These symptoms are often reversible with steroids or discontinuation of the causing agent.

Acute lymphoblastic leukemia

The CAR-T cell product tisagenlecleucel was approved by the US Food and Drug Administration (FDA) August 30, 2017, for children and young adults with ALL due to remarkable results in relapsed and refractory (R/R) ALL [1]. In this international study of 75 evaluable patients, the overall remission rate at 3 months was 81%, with a 12-month overall survival (OS) of 76%. The medium duration of remission was still not reported in the updated results, but the median OS was 19 months. In adult ALL, a similar construct was tested in 53 adults and induced complete remission in 83%, with a median OS of 12.9 months. However, patients with < 5% blasts in the bone marrow prior to CAR-T cell infusion had a median OS of 20.1 months [2]. Approval for adult leukemia is still pending, but expected in the near future.

The first CD22 CAR-T cell study in ALL was published in 2018 [3]. In a heavily pretreated group of 21 young/pediatric patients (age 7–30 years), the overall complete response (CR) rate was 57%. This study included patients previously treated with blinatumomab, CD19 CAR-T cells, and/or inotuzomab ozogamicin; 9 out of 10 patients in this group went into CR.

The most common adverse event (AE) after CAR-T cell therapy in general is CRS, with frequencies of 77–85% in the large studies [1, 2]. In the study by Maude et al. [1], 46% of patients were admitted to the ICU for treatment of CRS. In contrast, only 26% of patients had CRS grade 3+ in the study by Park et al. [2], which may reflect the differences in the study population (i.e., children vs. adults) or the criteria used to distinguish CRS from other similar reactions. Neurological symptoms, such as confusion, aphasia, and encephalopathy, were also common but not severe, and both CRS and neurological events were associated with high disease burden [2].

As an on-target off-tumor effect, all patients in the study by Maude et al. who responded to the treatment experienced long-lasting B cell aplasia with the need for immunoglobulin substitution [1].

Diffuse large B cell lymphoma

As B cell lymphoma cells express similar differentiation markers as B-ALL cells, similar approaches have been explored in these diseases. The second generation CD19 CAR-T cell product axicabtagene ciloleucel was approved by the FDA for R/R diffuses large B cell lymphoma (DLBCL). Phase II trials involving 101 treated patients resulted in an initial overall response rate (ORR) of 82%, with 40% still in CR after a median follow-up of 15.2 months [11]. Another CD19 CAR-T cell product, CTL019, achieved the best ORR of 59%, with a CR rate of 30% after 6 months, in 99 patients [12]. The third notable CD19 CAR-T cell product, JCAR 017, was tested in 68 R/R DLBCL patients and demonstrated the best ORR of 75% and 6-month CR of 37% [13]. The safety profiles were comparable in all three studies, with 80–90% experiencing grade 3+ AEs, predominantly neutropenia and anemia, and CRS occurring in > 90% of patients, though mostly with low grade symptoms.

CD20 is an established target for immunotherapy in B cell lymphomas and CD20 CAR T cells has been developed. Small studies have reported promising results on one or two patients in different lymphoma subtypes [39]. In a phase II a study recruiting patients with R/R NHL, primarily DLBCL, 9 of 11 patients had an objective response and 6 achieved CR [14]. Thus, CD20 seems just as promising a target as CD19 in lymphoma patients.

Table 1 Selected publication on immunotherapy in acute lymphoblastic leukemia and chronic lymphocytic leukemia

Name	Target/construct	Study type	*n*, population	Results	Adverse events	Reference
CAR-T therapy						
Tisangenlecleucel, CTL019	CD3/CD19 2nd gen CAR-T (4-1BB)	Phase II	75, RR-ALL children and young adults	Remission rate, 81% with all achieving MRD negativity	CRS grade 3+, 47%. Neurotoxic events grade 3 +, 10%	Maude et al. [1]
19-28z CAR T (MSKCC)	CD3/CD19 2nd gen CAR-T (CD28)	Phase II	53, RR-ALL Adults	Remission rate, 83% with 67% achieving MRD negativity	CRS grade 3+, 26%, one grade 5 CRS. Neurotoxic events grade 3 +, 42%	Park et al. [2]
CD22-CAR T (NIH)	CD3/CD22 2nd gen CAR-T (4-1BB)	Phase I dose escalation	21, RR-ALL children and young adults	ORR, 57%, with 42% achieving MRD negativity	MTD 1×10^6 cells/kg. DLT: Hypoxia. CRS grade 3+, 0%	Fry et al. [3]
Tisangenlecleucel, CTL019	CD3/CD19 2nd gen CAR-T (4-1BB)	Phase II	17, RR-CLL	ORR, 53%; CRR, 35%	CRS grade 3+, 20%	Porter et al. [4]
CD19 CAR T	CD3/CD19 3rd gen CAR-T (4-1BB, CD28)	Phase I/II	24, RR-CLL	ORR, 71%; CRR, 21%	CRS grade 3+, 8%, one grade 5 CRS.	Turtle et al. [5, 6]
CTL119	CD3/CD19 2nd gen CAR-T (4-1BB)	Pilot (+ibrutinib)	10, RR-CLL	CCR, 89%	CRS grade 3+, 10%	Gill et al. [7]
Bispecific antibodies						
Blinatumomab	CD3/CD19 bispecific T cell engager BiTE®	Phase III	405, RR-ALL Adults	Blinatumomab: median OS 7.7 months, CRR 34%. Chemotherapy: median OS 4.0 months, CRR 12%	Overall grade 3+ AE, 87% Mainly neutropenia and infections. CRS grade 3+, 5%. Neurotoxic events grade 3+, 9%	Kantarjian et al. [8]
Immune checkpoint inhibitors						
Nivolumab	Anti-PD-1 antibody	Phase II	25 RR/RT-CLL	RT-CLL: ORR, 44%; CRR, 11%	Overall grade 3+ AE, 60% (cytopenia and pulmonary events)	Ding et al. [9]
Pembrolizumab	Anti-PD-1 antibody	Phase I/II (+ibrutinib)	20 RT-CLL patients	ORR 60%, CRR 5%	Grade 3+ AE: cytopenia (24–57%), Overall grade 3+ immune-related events, 13.5%	Younes et al. [10]
Cancer vaccine therapy—no larger studies						

CAR chimeric antigen receptor, *RR* relapsed refractory, *ALL* acute lymphoblastic leukemia, *CLL* chronic lymphoblastic leukemia, *RT* Richter's transformation, *PFS* progression-free survival, *AE* adverse event, *CRS* cytokine release syndrome, *CRR* complete remission rate, *MRD* minimal residual disease, *ORR* overall response rate, *MTD* maximum tolerated dose

Table 2 Selected publication on immunotherapy in lymphoma

Name	Target/construct	Study type	*n*, population	Results	Adverse events	Reference
CAR-T therapy						
Axicabtagene ciloleucel, KTE-C19	CD3/CD28/CD19	Phase II	111, RR-DLBCL	ORR, 82%; CRR, 52%	Overall grade 3+ AE, 95%. Mainly neutropenia. CRS grade 3+, 13%. One grade 5	Neelapu et al. [11]
Tisangenlecleucel, CTL019 (Upenn)	CD3/4-1BB/CD19	Phase II	81, RR-DLBCL	ORR, 53%; CRR, 30%	Overall grade 3+ AE, 86%. CRS grade 3+, 23%. Neurotoxic events grade 3 +, 12%	Schuster et al. [12]
JCAR 017	CD3/4-1BB/CD19	Phase II	68, RR-DLBCL	ORR, 75%; CRR, 37%	CRS grade 3+, 1%. Neurotoxic events grade 3 +, 14%	Abramson et al. [13]
CD20 CAR T	CD3/4-1BB/CD20	Phase II	11, RR-NHL (DLBCL)	ORR, 82%; CRR, 55%	Overall grade 3+, 18%, CRS any grade, 0%	Zhang et al. [14]
Tisangenlecleucel, CTL019 (Upenn)	CD3/4-1BB/CD19	Case series	14, RR-FL	ORR, 79%; CRR, 71%	CRS grade 3+, 18%. Neurotoxic events grade 3 +, 11%	Schuster et al. [12]
Bispecific antibodies						
Blinatumomab	CD3/CD19 bispecific antibody	Phase II	21, RR-DLBCL	ORR, 43% CRR, 19%	Overall grade 3+ AE, 96%; neurotoxic events grade 3+, 22%	Viardot et al. [15]
(As above)	(As above)	Phase I	15, RR-FL	ORR, 80%; CRR, 40%	Overall grade 3+ AE, 90%; neurotoxic events grade 3+, 22%, 3 grade 5 events	Goebeler et al. [16]
(as above)	(As above)	Phase I	7, RR-MCL	ORR, 72%; CRR, 43%	(As above)	(As above)
AFM13	CD30/CD16A tetravalent chimeric antibody	Phase I	28, RR-HL	ORR, 12%; SD, 50%	Overall grade 3+ AE, 28% mostly pneumonia	Rothe et al. [17]
Immune checkpoint inhibitors						
Nivolumab	Anti-PD-1 antibody	Phase II	243, RR-HL	ORR, 69%; CR, 16%; 1-year OS, 92%	Serious AE, 12%; immune-mediated AEs: thyroiditis 12%	Armand et al. [18]
Pembrolizumab	Anti-PD-1 antibody	Phase II	210, RR-HL	ORR, 69%; CR, 22%; 9-month OS, 98%	Immune-related Aes: thyroiditis 12.5%	Chen et al. [19]
Pembrolizumab	Anti-PD-1 antibody	Phase I	17, RR-PMBCL	ORR, 41%; CRR, 12%	Overall grade 3+ AE, 12%; hypothyroidism among most common any grade AE	Zinzani et al. [20]
Nivolumab	Anti-PD-1 antibody	Phase I	11, RR-DLBCL	ORR, 36%; CRR, 18%	Overall grade 3+ AE, 22% (pneumonitis and cytopenia), 1 grade 5 event	Lesokhin et al. [21]
(as above)	(As above)	(As above)	10, RR-FL	ORR, 40%; CRR, 10%	(As above)	(As above)
(as above)	(As above)	(As above)	4, RR-MCL	ORR, 0%	(As above)	(As above)
(as above)	(As above)	(As above)	23, RR-TCL	ORR, 17%	(As above)	(As above)
Pembrolizumab	Anti-PD-1 antibody	Case series	7, NK/T-cell lymphoma	ORR, 100%; CRR, 71%	None grade 3+ AE	Kwong et al. [22]
Cancer vaccine therapy						
Mitumprotimut	Idiotype-KLH + GM-CSF	Phase III	349, treatment naive FL and RR-FL	No benefit compared to placebo	AEs low grade, similar to placebo	Freedman et al. [23]
Idiotype vaccine	hybridoma-isotype-KLH + GM-CSF	Phase III	177, treatment naive FL	No benefit compared to placebo	AEs low grade, similar to placebo	Schuster et al. [24]
MyVax	Idiotype-KLH + GM-CSF	Phase III	287, treatment naive FL	No overall benefit, IR-positive had significant longer PFS than controls	AEs low grade, similar to placebo	Levy et al. [25]

CAR chimeric antigen receptor, *NHL* non-Hodgkin lymphoma, *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *MCL* mantle cell lymphoma, *HL* Hodgkin lymphoma, *TCL* T cell lymphoma, *PMBCL* primary mediastinal B cell lymphoma, *RR* relapsed refractory, *OS* overall survival, *AE* adverse event, *CRS* cytokine release syndrome, *CRR* complete remission rate, *ORR* overall response rate, *MTD* maximum tolerated dose, *KLH* keyhole limpet hemocyanin, *GM-CSF* granulocyte macrophage colony stimulating factor, *IR* immune response

Table 3 Selected publication on immunotherapy in multiple myeloma

Name	Target/construct	Study type	*n*, Population	Results	Adverse events	Reference
CAR-T therapy						
CTL019 (Upenn)	CD19 CAR-T	Phase I after ASCT	10, MM, Early relapse after ASCT	2 out of 10 patients had longer PFS 2 than PFS1	1 grade I CRS	Garfall et al. [26]
mBCMA-CAR (NCI)	BCMA CAR-T	Phase I dose escalation	2, RR-MM	The two patients at highest dose level attained sCR and VGPR	Both patients had grade 3–4 CRS and prolonged cytopenia	Ali et al. [27]
huBCMA (Upenn)	BCMA CAR-T	Phase I dose escalation	21, RR-MM	RR 40–83%, depending on dose	Grade 3+ CRS, 29%; 1 grade 4 encephalopathy	Cohen et al. [29]
bb2121 (BluebirdBio Inc.)	BCMA CAR-T	Phase I dose escalation	20, RR-MM	ORR 89%, RR 100% at the higher doses	Grade 3+ CRS, 10%	Berdeja et al. [30]
LCAR-B38M (Nanjing Legend)	BCMA CAR-T	Phase I	19, RR-MM	ORR 100%. 32% MRD-negative sCR, and 32% nCR	Grade 3+ CRS, 11%	Fan et al. [31]
TCR-engineered T cells						
NY-ESO-1-LAGE-1	Antigens NY-ESO-1 and LAGE-1	Phase I/II (with ASCT)	20, mixed population of MM	70% CR or nCR	15% had grade 3 gastrointestinal GVHD. No cases of CRS	Rapoport et al. [32]
Immune checkpoint inhibitors						
Nivolumab	Anti-PD-1 antibody	Phase I	27, RR-MM	SD as best response	No MTD. 19% grade 3 AE	Lesokhin et al. [21]
Pembrolizumab	Anti-PD-1 antibody	Phase II (Pem/Pom/Dex)	48, RR-MM	ORR 60% (6% sCR, 2%CR, 19%VGPR, 33%PR)	Grade 3+ AE, 40%. Autoimmune events, 13% pneumonitis, 10% hypothyroidism	Badros et al. [33]
Cancer vaccine therapy						
DC-vaccine	Auto-DCs loaded with auto-MM cells	Phase I	12, RR-MM	1MR	No AEs above grade 2	Jung et al. [34]
DC-vaccine	Auto-DCs loaded with idiotype containing serum	Phase I	27, MM consolidation after ASCT	Median survival 5.3 vs. 3.4 years in consecutive control patients	AEs comparable to the clinical setting	Lacy et al. [35]
DC/MM fusion vaccine	Auto-DCs fused with auto-MM cells	Phase I	16, MM > 1 line of therapy	11 patients had disease stabilization	No AEs above grade 2	Rosenblatt et al. [36]
(As above)	(As above)	Phase II	36, MM consolidation after ASCT	Possible late improvement of response in 17% of patients	No possibly related AEs above grade 2	Rosenblatt et al. [37]
Bispecific antibodies—no studies reported						

CAR chimeric antigen receptor, *ASCT* autologous stem cell transplantation, *MM* multiple myeloma, *RR* relapsed refractory, *PFS* progression-free survival, *AE* adverse events, *CRS* cytokine release syndrome, *CR* complete remission (*n* near, *s* stringent), *MRD* minimal residual disease, *VGPR* very good partial response, *SD* stable disease, *ORR* overall response rate, *GVHD* graft versus host disease, *DC* dendritic cell, *MTD* maximum tolerated dose

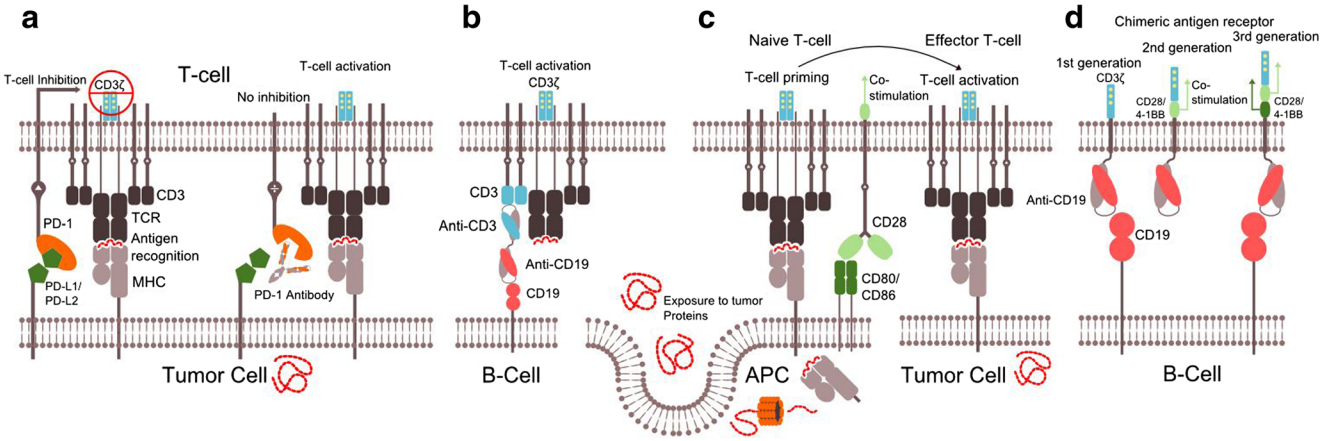

Fig. 1 Mechanism of immune activation by the major immunotherapy concepts. (A) T cells recognize tumor antigens through the TCR/MHC interaction, and if primed, the T cell starts the killing process of the tumor cell. However, if the T cell receives inhibitory signals from PD-L1 or PD-L2, the T cell is inactivated. Antibodies blocking the PD-1 stimulation, prevent the T cell inactivation, allowing the tumor killing process to proceed. (B) The activation through the TCR is mediated by CD3 and antibodies binding to CD3 can have an activating effect on the T cell. The CD3/CD19 bispecific antibodies bypass the antigen recognition step and activate the T cells in close relation to CD19 positive B cells. (C) Priming of T cells often needs co-stimulatory signals from antigen-presenting cells (APC) such as dendritic cells. When APC are exposed to large amounts of immunogenic tumor peptides they will present them for T cells and provide the co-stimulatory signals. This can be done in vitro by fusing APC with tumor cells or pulse APCs with tumor fragments, or in vivo with peptide vaccines. (D) Chimeric antigen receptor consists of a variable region of an antibody and the T cell activating CD3-zeta region. The genetic code for this receptor is transfected in to autologous T cells, expanded and re-infused in the patient. 2nd Generation CAR-T-cells have either CD28 or 4-1BB as a co-stimulatory region, and 3rd generation have both. PD-1, programmed death receptor 1; PD-L1/PD-L2, PD-1 ligand 1 and 2; TCR, T cell receptor; MHC, major histocompatibility complex; APC, antigen-presenting cell

Follicular lymphoma and mantle cell lymphoma

CTL019 has been tested in 14 heavily treated follicular lymphoma (FL) patients, demonstrating an ORR of 79%, with 71 in CR after 6 months [40]. Other studies including a small number of FL patients have demonstrated similarly encouraging results with an ORR of 80–100% [5, 41]. However, FL is often kept in check with less intensive strategies. Results from mantle cell lymphomas (MCL) are limited by very few patients in the reported studies, and the results vary between different studies. A larger phase II trial with the KTE019 construct is ongoing, and results are expected during 2018 (NCT02601313).

Chronic lymphocytic leukemia

In 17 evaluable R/R chronic lymphocytic leukemia (CLL) patients, the CTL019 construct induced an ORR of 53%, with a CR rate of 35% at a median follow-up of 9 months [4]. More recently, a third generation CD19 CAR-T cell product tested in 24 CLL patients induced an ORR of 71%, with a CR rate of 21% 4 weeks after infusion [6]. The BTK inhibitor ibrutinib approved for CLL has been shown to have an immune restorative effect and could be an interesting agent in combination with immunotherapy. This was confirmed preclinically, combining ibrutinib with CD19/CD3 CAR-T cells, and early clinical short-term results revealed a CR rate of 89% [7, 42]

T cell lymphoma and Hodgkin lymphoma

T cell lymphomas are rare and heterogeneous, complicating studies on novel drugs. In contrast to B cell aplasia which can be substituted with immunoglobulins, the lack of T cells is often fatal and no substitute is available. Furthermore, malignant T cells share an immunophenotype with the autologous T cells used for the CAR-T constructs, making them hard to distinguish from the neoplastic T cells. However, a group from Washington University developed a CD7-targeting CAR-T cells product with minimal self-recognition due to knock-out of CD7 expression on the CAR-T cells. They also deleted the alpha chain of the TCR in the transduced T cells to enable allogeneic application [43]. CAR-T cells targeting CD30 are being tested in Hodgkin lymphoma (HL) and some T cell lymphomas. Early results show some efficacy but are based on few patients, and a majority was refractory to brentuximab vedotin, which may be suboptimal for another CD30-targeting agent [44, 45].

Multiple myeloma

As myeloma cells are the malignant counterparts of mature plasma cells, they infrequently express CD19 [46]. However, relapses may arise from less differentiated, chemo-insensitive CD19-positive subpopulations [47]. Thus, a CD19-CAR-T cell product has been tested as consolidation therapy to salvage high-dose chemotherapy and autologous stem cell

transplantation (ASCT) [26]. Ten patients with relapse after ASCT underwent salvage ASCT, followed by CTL019 infusion 14–16 days later. The dose was 10-fold lower than in previous trials in ALL and CLL due to concerns regarding toxicity, and only one patient experienced grade 1 CRS. Two patients had longer progression-free survival (PFS) after ASCT+CD19-CAR-T cell treatment than after the initial ASCT. Compared to an historical control treated with salvage ASCT, the patients had longer PFS in this trial.

Another interesting target in MM is the B cell maturation antigen (BCMA), a member of the TNF receptor superfamily. BCMA is frequently expressed on myeloma cells, as well as plasmacytoid dendritic cells, normal plasma cells, and some memory B cells, but is absent from non-hematopoietic tissue and hematopoietic stem cells [48–51]. Second generation BCMA CAR-T cells have been developed, and the results of a phase I study and preliminary results of a phase II study in MM have been reported [27–29]. Responses and AEs were related to dose, and patients with PR or better had a higher peak of CAR-T cells and a reduction in soluble BCMA [28, 29]. Another BCMA CAR-T cell product (bb2121) is in a phase I dose-escalation trial (NCT02658929); results from 21 patients have been published. No DLTs occurred in these patients, and CRS occurred in 71% of patients. CRS was associated with higher dose levels but, in contrast to ALL, does not seem to be associated with tumor burden. The RR in patients treated with $\geq 150 \times 10^6$ cells was 94%. Nine of ten evaluable patients were MRD-negative [52].

The BMCA CAR-T cell product LCAR-B38M is being assessed in an ongoing study that has reported an ORR of 100% in 19 treated patients with CR and MRD-negativity in 6 patients. CRS was reported in 74% of patients and has been manageable, with one grade 3 and one grade 4 case, which recovered with treatment [31]. As considerable enthusiasm is felt in the field, several studies of BCMA CAR-T cells are underway.

Myeloma is one of the few indications in which T cells with an engineered TCR instead of CAR has been tested. In contrast to CAR-T cells, the TCR-engineered T cells can target MHC-presented peptides representing intracellular proteins, and have reduced the risk of CRS. The main disadvantage is the HLA-restriction of the TCR [38]. A phase I/II trial has tested an autologous T cell with an affinity-enhanced TCR against the cancer testis antigen NY-ESO-1 combined with standard melphalan high-dose chemotherapy. Twenty patients were enrolled, five of which relapsed after ASCT, and 12 patients had high-risk cytogenetic markers. The treatment was safe, with no CRS, despite an increase in serum IL-6. Three patients had grade 3 gastrointestinal autologous graft versus host disease (GVHD), and three patients had a rash that may have been a GVHD symptom possibly related to the engineered T cells. Of the 20 patients, 70% attained CR or near CR. An ongoing study has combined NY-ESO-1 TCR-transfected T cells with pembrolizumab (NCT03168438). A way to minimize GVHD could be via a transfection technique that simultaneously knocks out the endogenous TCRs, minimizing harmful combinations of endogenous alpha and beta chains [53]. As with newer CAR-T cell techniques aiming to disrupt TCR genes or beta-2-microglobulin genes, the technique may lead to a possible allogeneic off-the-shelf product [38].

Bispecific antibodies

Bispecific antibodies are antibodies with affinity to two different targets. A commonly used combination is the B cell marker CD19 with the T cell marker CD3, which brings the cytotoxic T cells in close proximity to the malignant B cells (Fig. 1(B)). New antibody constructs are being developed with variations in form and number of binding sites. Some have affinity to several different antigens such as the trispecific antibodies and others have an increased number of identical binding sites to increase avidity [54]. Blinatumomab, a bispecific T cell engager (BiTE®) specific for CD3and CD19, currently dominates this field, although a lot of new antibodies are being evaluated in ongoing trials. One drawback of Blinatumomab is the short half-life demanding continuous infusions, while other constructs with preserved Fc-domains have longer half-life.

Acute lymphoblastic leukemia

In July 2017, blinatumomab was approved for use in R/R B-ALL based on a randomized trial testing blinatumomab against standard chemotherapy. The trial included 405 patients and demonstrated an improved median OS of 7.7 months and CR rate of 34% in the blinatumomab arm vs. a median OS of 4.0 months and CR rate of 12% in the chemotherapy arm [8]. The FDA approval was recently expanded to include MRD-positive patients in remission after standard treatment. The approval was based on a single-arm study with 113 MRD-positive patients in which 88 (78%) achieved MRD-negativity after the addition of one cycle of blinatumomab [55]. Several different constructs have been tested in clinical trials, but the combination of CD3 and CD19 seems to be the focus in ALL [54].

In a phase III study, grade 3+ AEs were reported in 87% of patients treated with blinatumomab compared to 92% treated with chemotherapy. The most common AEs were neutropenia (38%) and infections (34%), but both were less frequent in the blinatumomab arm. Pyrexia has been the most reported AE, with an incidence of up to 80% but mainly low grade [56]. AEs of interest are CRS and neurological events, such as encephalopathy, confusion, and aphasia, but they occurred at low rates in this study, and neurological events were similar in

the two cohorts (9 vs. 8%). Three percent of patients were thought to have a fatal outcome related to blinatumomab, compared to 7% related to chemotherapy.

Non-Hodgkin lymphoma and CLL

In R/R DLBCL, blinatumomab has been shown to induce an objective response in 9 of 21 patients (43%), with 4 (19%) achieving CR [15]. Thirty-nine percent had to stop the treatment during stepwise dose escalation due to disease progression, and the authors speculated that a higher dose could have benefited these patients. However, a flat dose arm with the target dose was stopped after two patients due to neurological events. A phase I basket trial evaluated the safety and efficacy in different subtypes of non-Hodgkin lymphoma (NHL); 15 patients with FL had an OR of 80% and CR rate of 40%. In MCL, the OR was 72% and CR rate 43% [16]. These are encouraging results, but no long-term follow-up was reported on these patients. The activity of blinatumomab in CLL has only been explored in vitro and in murine studies but, despite its efficacy, no further trials have been reported [57].

Hodgkin lymphoma and T cell lymphoma

Both HL and T cell lymphomas often express CD30, and the toxin-conjugated anti-CD30 mAb brentuximab vedotin has approved indications in these diseases. Thus, bispecific CD30 antibodies have been tested in HL, but with limited responses. The tetravalent antibody specific for CD30 and CD16A was designed to activate natural killer cells instead of T cells and has been tested in 26 HL patients; 11.5% had a partial response and 50% had stable disease [17]. This construct is being tested in combination with the immune checkpoint inhibitor pembrolizumab and in CD30-positive T cell lymphomas (NCT02665650, NCT03192202).

Multiple myeloma

No results are available in MM, but several constructs involving CD3/BMCA and CD3/CD38 specific sites have completed preclinical evaluation and are now in clinical trials [50, 58–61].

Immune checkpoint inhibitors

T cells are regulated in both the priming phase and the effector phase. Immune checkpoint molecules on the T cell surface can shut down the activity of the cell if ligands to the receptor are present in sufficient amounts. In the priming phase, CTLA-4 has an important impact on regulating the activation of T cells. In the effector phase, the checkpoint molecule PD-1 on the T cell interacts with the ligands PD-L1 and PD-L2 on tumor cells and other cells in the microenvironment. Antibodies blocking the receptor or their ligands prevent the negative signal and preserve the activity of the T cells. The checkpoint ligands are often upregulated in the environment of tumors and on tumor cells, preventing spontaneous clearance by the immune system (Fig. 1(A)). The mentioned checkpoints are being targeted in an increasing number of malignancies, including hematological malignancies [62]. The regulatory mechanisms of immune activation and inhibition consist of a meshwork of proteins and pathways, and several other checkpoints are being targeted in preclinical and clinical trials.

Hodgkin lymphoma and primary mediastinal B cell lymphoma

The PD1 inhibitors nivolumab and pembrolizumab have been approved for HL due to encouraging clinical results. PD-L1 and PD-L2 are upregulated in HL, as well as in primary mediastinal B cell lymphoma (PMBCL) due to amplification of the gene region 9p24.1. In a study of 243 HL patients, 69% were reported to have objective responses to nivolumab, with 16% achieving CR and 53 achieving PR [18]. The median response duration was 16.6 months, and the 1-year OS was 92%. Very similar results were reported for 210 R/R HL patients treated with pembrolizumab, with an ORR of 69% and CR rate of 22.4%. The median OS and DOR were not reported, but the 9-month OS was reported to be 97.5% [19]. Several interesting trials are ongoing and include first-line approaches, and two phase III trials of note are NCT02684292, in which pembrolizumab is being tested directly against brentuximab, and NCT03138499, in which nivolumab is being tested with brentuximab vs. brentuximab alone. Despite the same gene amplification being present in PMBCL, the results have been more modest, with an ORR of 41% and CR of 11.7% in 17 evaluable patients, probably reflecting a more resistant lymphoma subtype in general [20].

Non-Hodgkin lymphomas

In a pooled phase 1 trial testing nivolumab as monotherapy in R/R lymphoid malignancies, 11 patients with DLBCL achieved an OR of 36%, with 18% achieving CR and 18% PR, representing the largest patient cohort for this disease [21]. The same study included ten patients with FL, three of whom had PR and one had CR with durable responses. In contrast, none of the four MCL patients responded, and larger datasets are not available for this disease. Twenty-three T cell lymphoma patients were included, with an OR of 17% (2 out of 13 patients with mycosis fungoides and 2 out of 5 patients with peripheral T cell lymphoma). Encouragingly, a retrospective report of seven patients with natural killer/T cell lymphoma demonstrated responses in all patients, and five patients were in CR after 6 months [22].

Chronic lymphocytic leukemia

Among CLL patients, only patients with Richter transformation (RT) seem to benefit from checkpoint inhibition. Pembrolizumab induced an objective response in 4 of 9 RT-CLL patients and no responses were observed in 16 CLL patients without RT [9]. Similar results were seen with nivolumab in combination with ibrutinib; only the RT patients had an increased benefit compared to ibrutinib alone [10]. Checkpoint inhibition in ALL is a limited field, but combinations with the other successful T cell-directed treatments are being explored, as the combination could be synergetic [63]. A case report demonstrated an anti-leukemic effect of low-dose nivolumab in two post-transplant ALL patients, but this is a daring field due to the increased risk of allogenic GVHD [64].

Multiple myeloma

Trials of immune checkpoint-blocking monoclonal antibodies (ICBs) have not produced as encouraging results in myeloma as in several types of lymphomas. In the basket trial of nivolumab as monotherapy for hematological malignancies, the best response for myeloma was stable disease (SD) (17 of 27 patients) [21]. The authors speculate that the known tumor heterogeneity and complex interactions with the tumor microenvironment could play a role in the lack of response. Compared to age-matched healthy donors and the non-clonal T cells in myeloma patients, the clonal tumor-infiltrating T cells were in a senescent state with low PD-1 expression, rather than an exhausted state with high PD-1 expression [65]. This implies that PD-1 blockade alone would not have an effect, even though the myeloma cells and microenvironment are PD-L1-positive.

Lenalidomide has a stimulating effect on T cells and natural killer cells and has been shown to enhance the effect of ICBs in vitro [66]. Thus, trials combining immunomodulatory imide drugs iMiDs and ICBs have been initiated. The initial reports from a phase I dose-escalation trial of pembrolizumab, lenalidomide, and low-dose dexamethasone, KEYNOTE-023 (NCT02036502), showed responses in 13 of 17 patients, with 4 VGPR and 9 PR, and manageable toxicity [67]. A phase II trial of pembrolizumab, pomalidomide, and low-dose dexamethasone included 48 R/R MM patients [33]; the ORR was 60% (6% sCR, 2% CR, 19% VGPR, 33% PR), a higher response rate than in studies with pomalidomide and dexamethasone alone. The addition of pembrolizumab to pomalidomide and dexamethasone seems to significantly improve the activity but at a significant cost in terms of the known ICB-associated autoimmune side effects. AEs possibly associated with pembrolizumab were pneumonitis ($n = 6$ cases), hypothyroidism ($n = 5$), adrenal insufficiency ($n = 2$), hepatitis ($n = 2$), and vitiligo ($n = 1$).

The phase I and II studies have paved the way for the two phase III pembrolizumab studies, KEYNOTE-185 (NCT02579863) with lenalidomide-dexamethasone and KEYNOTE-183 (NCT02576977) with pomalidomide-dexamethasone. Unfortunately, both of these studies showed an increased rate of death in the pembolizumab arm (19 vs. 9 in the lenalidomide study and 29 vs. 21 in the pomalidomide study), which led the FDA placing a full clinical stop on the trials as of July 3, 2017, including the ongoing phase I KEYNOTE-023.

Clinical trials with nivolumab-based combinations were also put on partial hold by the FDA. This partial hold has been lifted on the phase I CheckMate-039 testing nivolumab plus daratumumab (anti-CD38 mAb) with or without pomalidomide and dexamethasone, and on the phase II CA204142, a multiple cohort study including an arm with the anti-SLAMF7-mAb elotuzumab and lenalidomide. The three-armed phase III trial of pomalidomide dexamethasone with or without nivolumab and with or without elotuzumab is still on hold. Trials with combinations involving the anti-PD-L1-mAb durvalumab have similarly been put on full hold or partial hold.

Interestingly, one double refractory patient in the monotherapy nivolumab trial [21] went into ongoing CR for > 30 months on subsequent local radiotherapy against a bony plasmacytoma that developed while the patient was treated with nivolumab [68]. This suggests that ICBs may support an abscopal effect. Plans to study an effect of pembrolizumab with radiotherapy are under way (NCT03267888).

Vaccination therapy

Vaccination strategies attempt to boost immunological tumor killing by enhancing tumor antigen recognition and presentation. Numerous strategies are possible, as there are multiple steps in the immune-mobilizing process that can be optimized independently [69]. Central elements are the targeted antigen and its specificity for the tumor, the administration and accentuation of the chosen antigen, and use of an adjuvant to stimulate the desired immune response when the antigen is introduced. The principle of vaccination therapy is illustrated in Fig. 1(C). Several different antigens have been targeted within hematological malignancies, and several techniques have been utilized for antigen presentation, ranging from cell-based vaccines to peptide vaccines. In cell-based vaccines, the antigen-presenting cells are loaded with the selected antigens ex vivo or fused with tumor cells to ensure a broad antigen repertoire representing the tumor. Peptide vaccines consist of a few chosen antigens thought to be directly relevant to the tumor and administered in great numbers. The adjuvants vary in properties and are used for different methods. The most common adjuvants are Toll-like receptor ligands, GM-

CSF, and IL-12. Thus, vaccination therapy is a diverse and evolving field. One of the limitations of current vaccines is the immune inhibitory environment of most tumors, which is important to address in future studies.

Follicular lymphoma

Vaccines have generally been explored in indolent diseases with limited tumor burden, allowing time for the production of personalized vaccines and giving the vaccine optimal conditions in which to establish an immune response [69]. Thus, indolent lymphomas have been the center of attention, with results from three phase III trials in FL [23–25]. These vaccines were based on the idiotype of the malignant cells, which is the variable region of the B cell receptor and unique for the entire malignant B cell clone. The vaccines failed to show a clinical benefit in a randomized setting, but a subgroup evaluation in one study revealed that patients developing a vaccine-specific immune response (41%) had a significantly longer median PFS of 40 months than both controls and patients in the same arm with no immune response [25]. Unplanned subgroup analyses in another study revealed significantly longer disease-free survival for patients receiving IgM isotype rather than IgG vaccine isotypes compared to controls [24]. A major limitation of the idiotype vaccine is the unique B cell clone for each patient requiring a personal vaccine, which can have long production times of several months. Therefore, current development is focusing on more commonly shared targets. One such approach is the targeting of immune checkpoint ligands, such as PD-L1 and PD-L2, aiming at both the tumor cells and the immunosuppressive environment, which we are currently testing in FL (NCT03381768) [70]. Another broad, but individualized, approach is cell-based vaccines in which dendritic cells have been exposed to tumor cells to present a larger repertoire of antigens. Early clinical results have been reported for these approaches in a small number of FL and cutaneous T cell lymphoma patients, with some effect, but no recent reports are available [71, 72].

Chronic lymphocytic leukemia

In CLL, a similar strategy has been used in post-allogenic transplant patients in which the patients receive irradiated autologous tumor cells. Patients elicited specific immune responses with no increased GVHD and demonstrated a 2-year PFS of 82%, but without a comparable control [73]. A similar vaccine is currently being tested in untreated CLL patients in NCT01976520.

Multiple myeloma

Thus far, peptide-based vaccines for myeloma have not had encouraging results, which might rely the immune suppressive microenvironment of MM and the expression of PD-L1. [74] However, trials are ongoing and results pending. A classic dendritic cell-based vaccine study tested autologous dendritic cells loaded with irradiated autologous myeloma cells. The phase I trial enrolled 12 patients, with clinical data from nine patients treated with the highest dose of 10×10^6 cells weekly for 4 weeks. Seven of the nine patients had immunological responses. However, the clinical responses were modest with one minor response; five patients had stable disease, and three patients had progressive disease [34]. In a study from the Mayo Clinic, patients were vaccinated as consolidation after ASCT with autologous antigen-presenting cells, including dendritic cells loaded with autologous serum as a source of M-protein. The 27 treated patients had a longer median OS than 124 consecutive non-enrolled patients (5.3 vs. 3.4 years; $P = 0.02$). The study was not randomized [35]. A vaccine employing autologous dendritic cell/myeloma cells fused via treatment with polyethylene glycol (DC/MM fusion vaccine) has been tested in a phase I trial of patients with so-called active myeloma. Of 16 evaluable patients, 11 experienced disease stabilization after vaccination; 3 had ongoing stable disease at 12, 25, and 41 months. A phase II study of the DC/MM fusion vaccine was performed as consolidation after ASCT; 78% of patients attained CR or VGPR. The authors argued that because 17% of the patients had an improved depth of response to CR/nCR 100 days after transplantation (four from VGPR and two from PR) and after vaccination completion, this is consistent with an impact of the vaccine. An ongoing randomized multicenter phase II trial is testing the addition of this DC/MM fusion vaccine and GM-CSF to lenalidomide maintenance after ASCT (NCT02728102). As an attempt to overcome the immunosuppressive environment in MM, we are conducting a vaccination trial targeting PD-L1 (NCT03042793).

Conclusion

Treatments for lymphoproliferative diseases are undergoing a revolution after many years of work by resilient research groups. These treatments have come a long way, but much work is still needed. As the clinical relevance of immunotherapy is now firmly established, the costly work of improving the treatments is warranted. Furthermore, the treatments have to be tested against earlier lines of therapy and compared to traditional treatments, as they may be beneficial at an earlier stage of disease. Adding the T cell preserving ICBs to the T cell activating strategies is an obvious strategy not fully explored, and the parallel field of immune-modulating drugs and

small molecule inhibitors, which are known to have immune-restorative properties, could have a synergetic effect. Finally, biological features responsible for the response and resistance to treatment should be explored to allow us to offer the right combination at the right time to the right patient.

References

1. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, Qayed M, de Moerloose B, Hiramatsu H, Schlis K, Davis KL, Martin PL, Nemecek ER, Yanik GA, Peters C, Baruchel A, Boissel N, Mechinaud F, Balduzzi A, Krueger J, June CH, Levine BL, Wood P, Taran T, Leung M, Mueller KT, Zhang Y, Sen K, Lebwohl D, Pulsipher MA, Grupp SA (2018) Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 378(5):439–448
2. Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, Sauter C, Wang Y, Santomasso B, Mead E, Roshal M, Maslak P, Davila M, Brentjens RJ, Sadelain M (2018) Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med 378(5):449–459
3. Fry TJ et al (2018) CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med 24(1):20–28
4. Porter DL et al (2016) Randomized, phase II dose optimization study of chimeric antigen receptor (CAR) modified T cells directed against CD19 in patients (pts) with relapsed, refractory (R/R) CLL. J Clin Oncol 34:3009–3009
5. Turtle CJ, Hanafi LA, Berger C, Hudecek M, Pender B, Robinson E, Hawkins R, Chaney C, Cherian S, Chen X, Soma L, Wood B, Li D, Heimfeld S, Riddell SR, Maloney DG (Sep. 2016) Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med 8(355):355ra116
6. Turtle CJ, Hay KA, Hanafi LA, Li D, Cherian S, Chen X, Wood B, Lozanski A, Byrd JC, Heimfeld S, Riddell SR, Maloney DG (Sep. 2017) Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol 35(26):3010–3020
7. Gill S et al (2017) CD19 CAR-T cells combined with ibrutinib to induce complete remission in CLL. J Clin Oncol 35:7509–7509
8. 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 (2017) Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 376(9):836–847
9. Ding W, LaPlant BR, Call TG, Parikh SA, Leis JF, He R, Shanafelt TD, Sinha S, le-Rademacher J, Feldman AL, Habermann TM, Witzig TE, Wiseman GA, Lin Y, Asmus E, Nowakowski GS, Conte MJ, Bowen DA, Aitken CN, van Dyke DL, Greipp PT, Liu X, Wu X, Zhang H, Secreto CR, Tian S, Braggio E, Wellik LE, Micallef I, Viswanatha DS, Yan H, Chanan-Khan AA, Kay NE, Dong H, Ansell SM (Apr. 2017) Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. Blood 129(26):3419–3427
10. Younes A, Brody J, Carpio C, Lopez-Guillermo A, Ben-Yehuda D, Ferhanoglu AB, Nagler A, et al. (2017) Safety and efficacy of the combination of ibrutinib and nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukemia. Blood 130(Suppl 1):833
11. 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 (Dec. 2017) Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 377(26):2531–2544
12. Stephen SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jaeger U, et al. (2017) Primary analysis of Juliet: a global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma. Blood 130(Suppl 1):577
13. Jeremy AS, Palomba ML, Gordon LI, Lunning MA, Arnason JE, Wang M, Forero A, et al. (2017) High durable CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort. Blood 130(Suppl 1):581
14. Zhang W et al (2016) Treatment of CD20-directed chimeric antigen receptor-modified T cells in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an early phase IIa trial report. Signal Transduct Target Ther 1(1):16002
15. 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 (2016) Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. Blood 127(11):1410–1416
16. Goebeler M-E, Knop S, Viardot A, Kufer P, Topp MS, Einsele H, Noppeney R, Hess G, Kallert S, Mackensen A, Rupertus K, Kanz L, Libicher M, Nagorsen D, Zugmaier G, Klinger M, Wolf A, Dorsch B, Quednau BD, Schmidt M, Scheele J, Baeuerle PA, Leo E, Bargou RC (Apr. 2016) Bispecific T-cell engager (BiTE) antibody construct Blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study. J Clin Oncol 34(10):1104–1111
17. 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 (Jun. 2015) A phase 1 study of the bispecific anti-CD30/CD16A antibody construct AFM13 in patients with relapsed or refractory Hodgkin lymphoma. Blood 125(26):4024–4031
18. 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 (May 2018) 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 36(14):1428–1439
19. 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, for the KEYNOTE-087 (Jul. 2017) Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 35(19):2125–2132

20. Zinzani PL, Ribrag V, Moskowitz CH, Michot JM, Kuruvilla J, Balakumaran A, Zhang Y, Chlosta S, Shipp MA, Armand P (Jul. 2017) Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood 130(3):267–270
21. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, Millenson MM, Cohen AD, Schuster SJ, Lebovic D, Dhodapkar M, Avigan D, Chapuy B, Ligon AH, Freeman GJ, Rodig SJ, Cattry D, Zhu L, Grosso JF, Bradley Garelik MB, Shipp MA, Borrello I, Timmerman J (Aug. 2016) Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. J Clin Oncol 34(23): 2698–2704
22. Kwong Y-L, Chan TSY, Tan D, Kim SJ, Poon LM, Mow B, Khong PL, Loong F, Au-Yeung R, Iqbal J, Phipps C, Tse E (Apr. 2017) PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood 129(17):2437–2442
23. Freedman A, Neelapu SS, Nichols C, Robertson MJ, Djulbegovic B, Winter JN, Bender JF, Gold DP, Ghalie RG, Stewart ME, Esquibel V, Hamlin P (Jun. 2009) Placebo-controlled phase III trial of patient-specific immunotherapy with mitumprotimut-T and granulocyte-macrophage colony-stimulating factor after rituximab in patients with follicular lymphoma. J Clin Oncol 27(18):3036–3043
24. Schuster SJ, Neelapu SS, Gause BL, Janik JE, Muggia FM, Gockerman JP, Winter JN, Flowers CR, Nikcevich DA, Sotomayor EM, McGaughey DS, Jaffe ES, Chong EA, Reynolds CW, Berry DA, Santos CF, Popa MA, McCord AM, Kwak LW (Jul. 2011) Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma. J Clin Oncol 29(20):2787–2794
25. Levy R, Ganjoo KN, Leonard JP, Vose JM, Flinn IW, Ambinder RF, Connors JM, Berinstein NL, Belch AR, Bartlett NL, Nichols C, Emmanouilides CE, Timmerman JM, Gregory SA, Link BK, Inwards DJ, Freedman AS, Matous JV, Robertson MJ, Kunkel LA, Ingolia DE, Gentles AJ, Liu CL, Tibshirani R, Alizadeh AA, Denney DW Jr (Jun. 2014) Active idiotypic vaccination versus control immunotherapy for follicular lymphoma. J Clin Oncol 32(17):1797–1803
26. Garfall AL, Stadtmauer EA, Hwang WT, Lacey SF, Melenhorst JJ, Krevvata M, Carroll MP, et al (2018) Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. JCI Insight 3(8):e120505
27. Ali SA, Shi V, Maric I, Wang M, Stroncek DF, Rose JJ, Brudno JN, Stetler-Stevenson M, Feldman SA, Hansen BG, Fellowes VS, Hakim FT, Gress RE, Kochenderfer JN (2016) T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood 128(13):1688–1700
28. Cohen AD et al (2016) B-cell maturation antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) for multiple myeloma (MM): initial safety and efficacy from a phase I study. Blood 128(22):1147
29. Cohen AD et al (2017) Safety and efficacy of B-cell maturation antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) with cyclophosphamide conditioning for refractory multiple myeloma (MM). Blood 130(Suppl 1):505
30. Berdeja JG, Lin Y, Raje N, Munshi N, Siegel D, Liedtke M, Jagannath S, Maus MV, Turka A, Ping Lam A, Hege K, Morgan RA, Quigley MT, Kochenderfer JN (2017) Durable clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: updated results from a multicenter study of Bb2121 anti-Bcma CAR T cell therapy. Blood 130(Suppl 1):740
31. Fan FX et al (2017) Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma. J Clin Oncol 35(18_suppl): LBA3001
32. Rapoport AP, Stadtmauer EA, Binder-Scholl GK, Goloubeva O, Vogl DT, Lacey SF, Badros AZ et al (2015) NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific nntitumor effects in myeloma. Nat Med 21(8):914–921
33. Badros A, Hyjek E, Ma N, Lesokhin A, Dogan A, Rapoport AP, Kocoglu M, Lederer E, Philip S, Milliron T, Dell C, Goloubeva O, Singh Z (2017) Pembrolizumab, pomalidomide, and low-dose dexamethasone for relapsed/refractory multiple myeloma. Blood 130(10):1189–1197
34. Jung S-H, Lee HJ, Lee YK, Yang DH, Kim HJ, Rhee JH, Emmrich F, Lee JJ (2017) A phase I clinical study of autologous dendritic cell therapy in patients with relapsed or refractory multiple myeloma. Oncotarget 8(25):41538–41548
35. Lacy MQ, Mandrekar S, Dispenzieri A, Hayman S, Kumar S, Buadi F, Dingli D, Litzow M, Wettstein P, Padley D, Kabat B, Gastineau D, Rajkumar SV, Gertz MA (Dec. 2009) Idiotype-pulsed antigen-presenting cells following autologous transplantation for multiple myeloma may be associated with prolonged survival. Am J Hematol 84(12):799–802
36. Rosenblatt J, Vasir B, Uhl L, Blotta S, Macnamara C, Somaiya P, Wu Z et al (2011) Vaccination with dendritic cell/tumor fusion cells results in cellular and humoral antitumor immune responses in patients with multiple myeloma. Blood 117(2): 393–402
37. Rosenblatt J, Avivi I, Vasir B, Uhl L, Munshi NC, Katz T, Dey BR et al (2013) Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. Clinical cancer research: An Official Journal of the American Association for Cancer Research 19(13):3640–3648
38. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC (2018) CAR T cell immunotherapy for human cancer. Science 359(6382):1361–1365
39. Brudno JN, Kochenderfer JN (Aug. 2017) Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol 15(1):31–46
40. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, Brogdon JL, Pruteanu-Malinici I, Bhoj V, Landsburg D, Wasik M, Levine BL, Lacey SF, Melenhorst JJ, Porter DL, June CH (Dec. 2017) Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med 377(26):2545–2554
41. Kochenderfer JN, Somerville RPT, Lu T, Shi V, Bot A, Rossi J, Xue A, Goff SL, Yang JC, Sherry RM, Klebanoff CA, Kammula US, Sherman M, Perez A, Yuan CM, Feldman T, Friedberg JW, Roschewski MJ, Feldman SA, McIntyre L, Toomey MA, Rosenberg SA (Jun. 2017) Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol 35(16):1803–1813
42. Fraietta JA, Beckwith KA, Patel PR, Ruella M, Zheng Z, Barrett DM, Lacey SF, Melenhorst JJ, McGettigan SE, Cook DR, Zhang C, Xu J, Do P, Hulitt J, Kudchodkar SB, Cogdill AP, Gill S, Porter DL, Woyach JA, Long M, Johnson AJ, Maddocks K, Muthusamy N, Levine BL, June CH, Byrd JC, Maus MV (Mar. 2016) Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. Blood 127(9):1117–1127
43. Cooper ML, Choi J, Staser KW, Ritchey J, Niswonger J, Eckardt K, Rettig MP, et al (2017) An 'off-the-Shelf' fratricide-resistant CAR-T for the treatment of T cell hematologic malignancies. Blood 130(Suppl 1):844

44. Ramos CA, Ballard B, Liu E, Dakhova O, Mei Z, Liu H, Grilley B, et al (2015) Chimeric T cells for therapy of CD30+ Hodgkin and non-Hodgkin lymphomas. Blood 126(23):185
45. Wang C-M, Wu ZQ, Wang Y, Guo YL, Dai HR, Wang XH, Li X, Zhang YJ, Zhang WY, Chen MX, Zhang Y, Feng KC, Liu Y, Li SX, Yang QM, Han WD (Mar. 2017) Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase I trial. Clin Cancer Res 23(5):1156–1166
46. Swerdlow SH et al (2017) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4t, Lyon
47. Paiva B et al (Feb. 2017) Differentiation stage of myeloma plasma cells: biological and clinical significance. Leukemia 31(2):382–392
48. Darce JR, Arendt BK, Wu X, Jelinek DF (2007) Regulated expression of BAFF-binding receptors during human B cell differentiation. J Immunol 179(11):7276–7286
49. Tai YT, Mayes PA, Acharya C, Zhong MY, Cea M, Cagnetta A, Craigen J, Yates J, Gliddon L, Fieles W, Hoang B, Tunstead J, Christie AL, Kung AL, Richardson P, Munshi NC, Anderson KC (2014) Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood 123(20):3128–3138
50. Seckinger A, Delgado JA, Moser S, Moreno L, Neuber B, Grab A, Lipp S, Merino J, Prosper F, Emde M, Delon C, Latzko M, Gianotti R, Lüoend R, Murr R, Hosse RJ, Harnisch LJ, Bacac M, Fauti T, Klein C, Zabaleta A, Hillengass J, Cavalcanti-Adam EA, Ho AD, Hundemer M, San Miguel JF, Strein K, Umaña P, Hose D, Paiva B, Vu MD (2017) Target expression, generation, preclinical activity, and pharmacokinetics of the BCMA-T cell bispecific antibody EM801 for multiple myeloma treatment. Cancer Cell 31(3):396–410
51. Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, Gress RE, Hakim FT, Kochenderfer JN (2013) B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res 19(8):2048–2060
52. Raje N et al (2018) bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: updated results from a multicenter phase I study. J Clin Oncol 36:abst 8007
53. Mastaglio S, Genovese P, Magnani Z, Ruggiero E, Landoni E, Camisa B, Schiroli G, Provasi E, Lombardo A, Reik A, Cieri N, Rocchi M, Oliveira G, Escobar G, Casucci M, Gentner B, Spinelli A, Mondino A, Bondanza A, Vago L, Ponzoni M, Ciceri F, Holmes MC, Naldini L, Bonini C (2017) NY-ESO-1 TCR single edited stem and central memory T cells to treat multiple myeloma without graft-versus-host disease. Blood 130(5):606–618
54. Viardot A, Bargou R (2018) Bispecific antibodies in haematological malignancies. Cancer Treat Rev 65:87–95
55. Gökbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, Diedrich H, Topp MS, Brüggemann M, Horst HA, Havelange V, Stieglmaier J, Wessels H, Haddad V, Benjamin JE, Zugmaier G, Nagorsen D, Bargou RC (Apr. 2018) Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 131(14):1522–1531
56. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, Bader P, O'Brien MM, Brethon B, Bhojwani D, Schlegel PG, Borkhardt A, Rheingold SR, Cooper TM, Zwaan CM, Barnette P, Messina C, Michel G, DuBois SG, Hu K, Zhu M, Whitlock JA, Gore L (Dec. 2016) Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 34(36):4381–4389
57. Robinson HR, Qi J, Baskar S, Cook E, Ahn IE, Herman SEM, Rader C, Wiestner A (2017) Activity of CD19/CD3 bispecific antibodies in chronic lymphocytic leukemia. Blood 130(Suppl 1):799
58. Hipp S, Tai YT, Blanset D, Deegen P, Wahl J, Thomas O, Rattel B, Adam PJ, Anderson KC, Friedrich M (Aug. 2017) A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo. Leukemia 31(8):1743–1751
59. de Zafra C, Balazs M, Fajardo F, Liang L, Zhong W, Henn A, Bernett MJ, et al (2017) Preclinical characterization of AMG 424, a novel humanized T cell-recruiting bispecific anti-CD3/CD38 antibody. Blood 130(Suppl 1):500
60. Chu SY, Miranda Y, Phung S, Chen H, Rashid R, Endo NA, Chan ET, et al (2014) Immunotherapy with long-lived anti-CD38 × anti-CD3 bispecific antibodies stimulates potent T cell-mediated killing of human myeloma cell lines and CD38+ cells in monkeys: a potential therapy for multiple myeloma. Blood 124(21):4727
61. Moore GL, Lee SH, Schubbert S, Miranda Y, Rashid R, Pong E, Phung S, et al (2015) Tuning T cell affinity improves efficacy and safety of anti-CD38 × anti-CD3 bispecific antibodies in monkeys - a potential therapy for multiple myeloma. Blood 126(23):1798
62. Ok CY, Young KH (Dec. 2017) Checkpoint inhibitors in hematological malignancies. J Hematol Oncol 10(1):103
63. Maude SL, Hucks GE, Seif AE, Talekar MK, Teachey DT, Baniewicz D, Callahan C, et al (2017) The effect of pembrolizumab in combination with CD19-targeted chimeric antigen receptor (CAR) T cells in relapsed acute lymphoblastic leukemia (ALL). J Clin Oncol 35(15):103
64. Chan TSY, Sim JPY, Kwong Y-L (Sep. 2017) Low-dose nivolumab-induced responses in acute lymphoblastic leukaemia relapse after allogeneic haematopoietic stem cell transplantation. Ann Hematol 96(9):1569–1572
65. Suen H, Brown R, Yang S, Weatherburn C, Ho PJ, Woodland N, Nassif N, Barbaro P, Bryant C, Hart D, Gibson J, Joshua D (Aug. 2016) Multiple myeloma causes clonal T-cell immunosenescence: identification of potential novel targets for promoting tumour immunity and implications for checkpoint blockade. Leukemia 30(8): 1716–1724
66. Görgün G, SamurMK, Cowens KB, Paula S, Bianchi G, Anderson JE, White RE, et al (2015) Lenalidomide enhances immune checkpoint blockade-induced immune response in multiple myeloma. Clin Cancer Res 21(20):4617–18
67. Mateos M-V et al (2016) Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): final efficacy and safety analysis. |2016 ASCO Annual Meeting|Abstracts|eeting Library, J Clin Oncol (ASCO Anu. Meet.), vol 34, p. 34: abstr 8010
68. Pianko MJ, Funt SA, Page DB, Cattry D, Scott EC, Ansell SM, Borrello IM, Gutierrez M, Lendvai N, Hassoun H, Landgren CO, Lesokhin AM (2018) Efficacy and toxicity of therapy immediately after treatment with nivolumab in relapsed multiple myeloma. Leuk Lymphoma 59(1):221–224
69. Nahas MR, Rosenblatt J, Lazarus HM, Avigan D (2018) Anti-cancer vaccine therapy for hematologic malignancies: an evolving era. Blood Rev 32(4):312–25
70. Andersen MH (Sep. 2015) Immune regulation by self-recognition: novel possibilities for anticancer immunotherapy. J Natl Cancer Inst 107(9):djv154
71. Di Nicola M et al (2009) Vaccination with autologous tumor-loaded dendritic cells induces clinical and immunologic responses in indolent B-cell lymphoma patients with relapsed and measurable disease: a pilot study. Blood 113(1):18–27
72. Maier T, Tun-Kyi A, Tassis A, Jungius KP, Burg G, Dummer R, Nestle FO (Oct. 2003) Vaccination of patients with cutaneous T-cell

lymphoma using intranodal injection of autologous tumor-lysate-pulsed dendritic cells. Blood 102(7):2338–2344

73. Burkhardt UE, Hainz U, Stevenson K, Goldstein NR, Pasek M, Naito M, Wu D, Ho VT, Alonso A, Hammond NN, Wong J, Sievers QL, Brusic A, McDonough SM, Zeng W, Perrin A, Brown JR, Canning CM, Koreth J, Cutler C, Armand P, Neuberg D, Lee JS, Antin JH, Mulligan RC, Sasada T, Ritz J, Soiffer RJ, Dranoff G, Alyea EP, Wu CJ (Sep. 2013) Autologous CLL cell vaccination early after transplant induces leukemia-specific T cells. J Clin Invest 123(9):3756–3765
74. Yousef S, Marvin J, Steinbach M, Langemo A, Kovacsovics T, Binder M, Kröger N, Luetkens T, Atanackovic D (2015) Immunomodulatory molecule PD-L1 is expressed on malignant plasma cells and myeloma-propagating pre-plasma cells in the bone marrow of multiple myeloma patients. Blood Cancer J 5(3):e285