Next generation immunotherapies for lymphoma: one foot in the future

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Abstract

Improved understanding of the interactions between cancer cells and the immune system combined with technological advances has led to the development of novel types of immunotherapies. These include checkpoint inhibitors (CPI), T cell engager antibodies (TCE), and Chimeric Antigen Receptor (CAR)-T cells which have demonstrated remarkable efficacy in B-cell malignancies, including anti-PD1 antibodies in Hodgkin lymphoma, and TCE and CAR-T cells in B-ALL, leading to their approval in these indications. Recent clinical data suggest that these immunotherapies may also benefit patients with other types of hematologic malignancies, particularly patients with Hodgkin and non-Hodgkin lymphomas. Here, we review the most recent clinical data regarding these different immunotherapies in patients with lymphoma. Ongoing and future studies should further define which immunotherapy may best apply to a given patient in order to provide a "personalized immunotherapy".

Keywords: Immunotherapy, Lymphoma, Checkpoint inhibitors, Bispecific antibodies, CAR-T cells.

Key message: Novel types of immunotherapies are arising for the treatment of B-cell malignancies which include checkpoint inhibitors, T cell engager antibodies, and Chimeric Antigen Receptor (CAR)-T cells. Here, we review the most recent clinical data regarding these immunotherapies in patients with lymphoma and envision how they may be integrated in future therapeutic strategies.

Introduction

The complex relationship between the immune system and cancer development has been the subject of investigation for decades. In recent years, crucial advances have been made in this field. This progress, combined with technological advances, has led to the development of novel immunotherapies which have demonstrated remarkable efficacy for the treatment of cancer. In lymphoid malignancies, three of these new immunotherapies appear to be particularly promising: immune checkpoint inhibitors (CPI), T-cell engager antibodies (TCE) and Chimeric Antigen Receptor (CAR) T cells. Each of these approaches has its own advantages and inconveniences (Table 1). Some of these immunotherapies have already been granted approval by the FDA for hematologic malignancies (anti-PD1 antibodies in Hodgkin lymphoma, TCE and CAR T cells in B-ALL). In the future, these approvals are likely to be extended to other malignancies, including Hodgkin and non-Hodgkin lymphomas. In this review, we analyze the most recent clinical data regarding these different immunotherapies in patients with lymphoma.

Checkpoint inhibitors

Checkpoint inhibitors (CPI) are monoclonal antibodies (Ab) that block T cell inhibitory signals. They can "reinvigorate" a pre-existing antitumor immune response by releasing the breaks from tumor immunosuppression. These therapies are unique because they do not target directly the tumor cells but rather the immune system. This explains why the same CPI may be used for the treatment of various cancers. To date, six CPIs have been approved by the FDA for the treatment of cancer: one anti-CTLA4 antibody (ipilimumab), two anti-PD1 antibodies (nivolumab, pembrolizumab) and three anti-PDL1 antibodies (atezolizumab, avelumab and durvalumab).

These CPI exhibit toxicities which are different from those observed with chemotherapy or other anti-tumor agents. These toxicities are characterized by the occurrence of immune-related adverse events (irAEs) which are frequent (up to 90% of patients) although usually mild. However, in some cases, these irAEs may be severe and sometimes life-threatening, particularly with anti-CTLA4 Abs (5 to 20% of grade ≥ 3 adverse events in monotherapy)[1]. Luckily, most of these irAEs are reversible although some may be definitive (e.g. endocrine disorders). Following encouraging results on solid tumors, these CPIs were also evaluated in patients with lymphoma (Table 2).

Hodgkin lymphoma

To date, Hodgkin lymphoma (HL) is the most sensitive cancer to anti-PD1 antibodies. This may be explained by the fact that the Reed-Sternberg cells (RSC) constantly express the ligand for PD1 (PD-L1 ligand). This constitutive expression of PD-L1 may result from two mechanisms: 1) Genetic alterations in 9p24 which are found in 97% of RSC in HL[2]. This amplicon contains the PD-L1 and PD-L2 genes which are then directly amplified and overexpressed. It also contains the JAK2 gene which, indirectly, also induces the transcription of the PDL1 and PDL2 genes; and 2) EBV infection (present in about 40% of HL tumors) induces PD-L1 expression *via* the viral protein LMP1[3]. Interestingly, some clinical evidence suggests a positive correlation between the level of PD-L1 expression by the RSC and the efficacy of nivolumab in HL patients[4]. However, the mechanism of action of anti-PD1 antibodies in Hodgkin lymphoma remains incompletely elucidated as the Reed-Sternberg cell have frequently lost the expression of class I (usually by loss/mutation of the β2 microglobulin gene[5]) and/or class II HLA, theoretically compromising their recognition by T cells[6–8].

The first trials evaluating anti-PD1 Abs in HL were performed on small numbers of patients (23 and 31 patients, respectively). All these patients had been heavily pre-treated (the majority of them had received prior treatment with brentuximab-vedotin (BV) and/or autologous hematopoietic stem cell transplantation [HSCT]). Nevertheless, the results were dramatic, showing tumor regression in almost all patients[9,10]. These results were confirmed in a study which evaluated nivolumab in 80 HL patients who had relapsed after autologous HSCT and BV[4]. To date, the two largest studies testing anti-PD1 Abs in Hodgkin lymphoma are CHECKMATE-205 (N=243 patients treated with nivolumab)[11] and KEYNOTE-087 (N=210 patients treated with pembrolizumab)[12]. These studies, which represent more than 450 patients in total, showed overall response rates around 70% and complete remission (CR) rates around

20%. There appears to be no clear differences in efficacy according to the treatments previously received (BV and/or autologous HSCT) or between nivolumab and pembrolizumab (provided these studies were not meant to be comparative). These results led to the approval by the FDA of nivolumab and pembrolizumab in relapsed or refractory Hodgkin lymphoma in May 2016 and March 2017, respectively.

Although the response rates to anti-PD1 are very important in HL, a significant proportion of patients seem to escape secondarily, particularly those who have not reached a CR. Indeed, the latest results of CHECKMATE-205 study showed that for patients in CR, the median duration of response was not reached after a median follow-up of 15 months whereas for patients in partial response (PR), the median duration of response was 13 months (cohort B)[13]. The question therefore arises whether, in these patients, the treatment with anti-PD1 should be continued (for how long?) exposing the patients to the risk of tumor escape and progression, or whether these patients should be consolidated with an allogenic-HSCT exposing the patients to an increased risk of toxicities. Indeed, a non-comparative, retrospective study by Merryman et al suggested that patients undergoing allogenic-HSCT who had been previously treated with anti-PD1 Abs might experience more toxicities compared to historical controls, notably a possible increased risk of sinusoidal obstruction syndrome (SOS) and acute graft-versus-host disease (aGVHD), sometimes fatal[14]. A significant proportion of patients also developed a "non-infectious febrile syndrome". Interestingly, relapse rates appeared to be lower in patients who have received anti-PD1 treatment prior to allogenic-HSCT compared to historical controls. In a recent publication by Beköz et al, 11 patients treated by nivolumab received allogenic-HSCT. Three patients developed skin GVHD, one patient experienced chronic lung GVHD, and two patients died[15]. Two studies focused on patients treated with anti-PD1 after allogenic-HSCT[16,17]. These studies showed that treatment with anti-PD1 may cause or reactivate GVHD. These GVHD usually occur early (i.e. within weeks), are often steroid-refractory and are accompanied by a high mortality-rate. However, the anti-tumor efficacy of anti-PD1 after allogenic-HSCT seems very good with objective response rates comprised between 79 and 95% (including 42-50% complete responses) and prolonged PFS. Thus, PD-1 blockade before or after an allogenic-HSCT may be associated with an increased toxicity and efficacy. However, the data available in these situations remain very limited and one should be very cautious not to draw premature conclusions. More studies are needed to better determine how these two therapies may be optimally combined (and define in which order) and how their toxicities should be better managed.

Avelumab is an anti-PDL1 antibody which function is substantially different from anti-PD1 Abs. This antibody is directed against the tumor cells (and the PDL1-expressing immunosuppressive cells from the microenvironment) in order to block the PD1-PDL1 interaction. *In vitro*, avelumab induces antibody-dependent cellular cytotoxicity (ADCC) *via* its IgG1 constant domain. Additionally, it does not block the interaction between PD1 and its other ligand, PDL2. Avelumab's efficacy in Hodgkin lymphoma may be reduced compared to anti-PD1 antibodies due to i) the absence of PDL2 blockade and ii) its shorts half-life (6 days vs ≈26 days for nivolumab and pembrolizumab). A preliminary phase 1b trial testing avelumab in 31 patients with relapsed/refractory Hodgkin lymphoma showed an overall response rate of 42%, including 16% complete responses[18]. Two other anti-PDL1 antibodies are also being tested in lymphoma: atezolizumab in monotherapy in patients with relapsed or refractory HL (NCT03120676) and durvalumab in monotherapy (NCT03241017) and in combination (Table 3) in patients with non-Hodgkin Lymphoma.

Numerous combination studies are also in progress to improve or prolong anti-PD1 efficacy (Table 3). The immunologic rationale for combining them with other anticancer agents is described in Table 7. In particular, two studies are testing the combination of nivolumab and brentuximab vedotin. Intermediate results of these studies were reported at ICML 2017[19,20] and one was recently published[21]. In these studies, complete response rates were particularly high (61 and 63%, respectively). Another study (CheckMate 039) tested the combination of nivolumab and ipilimumab[22]. Of the 31 patients with Hodgkin lymphoma, the overall response rate was 74%, including 19% CR. These results are substantially similar to what is expected with nivolumab monotherapy.

Non-Hodgkin lymphomas

Checkpoint inhibitors were also tested in non-Hodgkin lymphomas (NHL), including anti-CTLA4 and anti-PD1 Abs (Table 2). A dose escalation phase I trial evaluated ipilimumab (anti-CTLA4) in patients with refractory or relapsed NHL. Among 18 patients, there were 2 objective responses: one PR in a patient with follicular lymphoma and one prolonged CR (ongoing at 31 months) in a patient with diffuse large B-cell lymphoma (DLBCL)[23]. Ipilimumab was also tested in 29 cancer patients who had relapsed after an allogenic-HSCT. Patients received one injection of ipilimumab at a dose of 0.1 to 3 mg/kg[24]. Among patients with lymphoid malignancies, two CR (2 HL) and one PR (1 mantle cell lymphoma) were observed. No response was observed in patients with chronic lymphocytic leukemia (N=2) nor myeloma (N=6). Another study tested repeated and higher doses (3 and 10mg/kg) of

ipilimumab in patients hematologic malignancies who had relapsed after allogeneic-HSCT[25]. Among patients who received ipilimumab at 10 mg/kg (N=22), there were 5 CR (4 AML and 1 MDS), 2 PR (1 HL and 1 plasmacytoma) and 6 tumor regressions (2 AML, 3 HL and 1T-NHL). Of note, 6 patients (21%) experienced GVHD.

The anti-PD1 Ab, nivolumab, was evaluated in 81 patients with relapsed or refractory lymphoid malignancies, including 10 follicular lymphoma and 11 DLBCL[26]. In these patients, the overall response rates were 40% (1 CR and 3 PR) and 36% (2 CR and 2 PR), respectively. However, these results need to be interpreted with caution due to the very small number of patients. The ongoing phase II trial, Checkmate-139, should help clarify the actual efficacy anti-PD1 Abs in DLBCL.

Interestingly, some subsets of NHL may be particularly sensitive to anti-PD1 therapy. These include NHL with 9p24 genetic alterations (which is not restricted to HL) and lymphomas which are associated with EBV, which frequently express PDL1[27]. The 9p24 genetic alterations can be found in about half of the primary mediastinal B-cell lymphomas (PMBL), primary CNS lymphomas and testicular lymphomas whereas it is found in only 6% of DLBCL[28]. KEYNOTE-013 (NCT01953692) evaluated the efficacy of pembrolizumab (anti-PD1) in PMBL[29]. In this study, the overall response rate was 41% (7/17 patients). These results led to an extended multicenter phase II study (KEYNOTE-170, NCT02576990) which intermediate results were presented at ICML 2017. Among 29 evaluable patients, the overall response rate was 41% including 4 complete responses (14%)[30]. Another anti-PD1, nivolumab was also tested in a small series of 5 patients with relapsed or refractory primary CNS lymphoma (N=4) or testicular lymphoma with CNS relapse (N=1)[31]. All patients experienced an objective response, including 4 CR, 3 of whom remained progression-free at 13^{+} to 17^{+} months. These data suggest that immunotherapy may also be effective in so-called "immuno-privileged" sites.

Pembrolizumab was tested in 25 patients with relapsed or refractory chronic lymphocytic leukemia (CLL) (N=16) or Richter syndrome (RS) (N=9)[32]. None of CLL patients responded but 4 out of 9 RS patients (44%) experienced an objective response including 1 CR. RS may be particularly sensitive to anti-PD1 therapy because it is known to have a high degree of genetic instability (≈50% TP53 disruption) and an increased expression of PDL1.

Anti-PD1 may also be effective in T-NHL although one may be concerned about a potential stimulatory effect of CPI on tumor T cells. Pembrolizumab was tested in 24 patients with

relapsed or refractory mycosis fungoides or Sezary syndrome (SS). The overall response rate was 38% (1 complete response and 8 partial responses)[33]. A "skin-flare" reaction was observed in some patients (8/15, all SS), which did not correlate with tumor response nor progression. NK/T lymphomas may also respond to PD1-blockade. This lymphoma is constantly associated with EBV and its prognosis is poor in case of relapse after treatment with L-asparaginase (median OS=3-4 months). Pembrolizumab was initiated in 7 patients with relapsed or refractory T/NK lymphoma. All patients experienced an objective response, including 5 CR[34].

Similar to Hodgkin lymphomas, numerous combination studies are in progress in non-Hodgkin lymphomas to further improve these results (Table 3 & 7). Of note, trials combining anti-PD1 Abs with lenalidomide, an immunomodulatory drug, have been recently placed on hold by the FDA because of a death rate higher than expected (KEYNOTE- 183 and -185). Safety evaluations of these combinations are still ongoing.

T-Cell Engager antibodies

T-cell engager antibodies are immunoglobulin fragments capable of recognizing 2 antigens: one located on the tumor cells (e.g. CD19) and one on the T cells (e.g. CD3). This double recognition is meant to recruit and activate T cells in contact with the tumor and trigger tumor cell destruction by the T cells. Blinatumomab (Amgen®), an anti-CD19/CD3 bispecific Ab, was the first TCE antibody to demonstrate efficacy in the clinic. Blinatumomab has been shown to be effective in relapsed and refractory acute lymphoblastic leukemia (B-ALL)[35,36]. In 2014, blinatumomab was approved by the FDA in this indication. Following these encouraging results, blinatumomab as well as other TCEs have been evaluated in patients with lymphoma (Table 4).

Non-Hodgkin lymphoma

A Phase I study evaluated blinatumomab in 76 patients with relapsed or refractory B-NHL[37]. As for ALL, blinatumomab was administered in continuous infusions (over several weeks) given its very short half-life (2 hours). However, the dose used in NHL was much higher than the one used in ALL (60µg/m2/day vs 28µg/d). Beyond this dose, there is a limiting neurological toxicity. In this study, at the optimal dose, the overall response rate was 69% for all B-NHL patients (N = 35) and 55% for DLBCL (N = 11). A phase II study reported by Viardot et al. evaluated blinatumomab in patients with relapsed or refractory DLBCL[38]. Of the 21 evaluable patients, the overall response rate was 43%, including 19% CR, some of

which were prolonged. A phase II/III study is currently underway to compare blinatumomab with conventional (investigator-selected) treatment in patients with relapsed or refractory aggressive NHL in incomplete response after salvage therapy (NCT02910063). Blinatumomab is also evaluated in combination with lenalidomide in relapsed or refractory NHL (NCT02568553).

Other TCE antibodies are also being tested in NHL. REGN1979, a new CD20/CD3 bispecific TCE, was evaluated in a phase I trial. The preliminary results, presented at ASH 2016, seem to show moderate efficacy with an overall response of 20% (N=20), although dose escalation is still ongoing[39]. FBTA05 is a CD20/CD3 « trifunctional » TCE with a preserved IgG1-like constant domain. It was evaluated in a phase I/II trial in combination with donor lymphocyte infusion for the treatment of patients with NHL who had relapsed after allogenic-HSCT (NCT01138579). This molecule had shown promising results in a phase I for pediatric patients with B lymphoid malignancies (NHL, Burkitt lymphoma, ALL) leading to 9 objective responses out of 10 patients, including 5 CR[40].

Hodgkin lymphoma

The Reed-Sternberg cells strongly express CD30 which makes it a target of choice for antibody recognition. AFM13, a tetrameric bispecific antibody (TandAb®) presenting two anti-CD30 domains and two anti-CD16A domains, was developed in order to recruit and activate NK cells *via* FcγRIII (CD16) at the tumor site. A phase I trial evaluated increasing doses of AFM13 (weekly infusions) in 26 patients with relapsed or refractory Hodgkin lymphoma[41]. The overall response rate was 23% with a dose-dependent efficacy. A phase II is currently underway (NCT02321592).

Chimeric Antigen Receptor T Cells

CAR-T cells have been in clinical development since the late 1990's, initially in solid tumors. CAR-T cells are T cells which have been genetically modified and expanded *ex vivo* after apheresis. These T cells are engineered to express a chimeric antigen receptor which allows them to be "redirected" against the tumor cells. The chimeric receptor is a transmembrane protein composed of the Ag-recognition domain of an antibody for the extracellular part, a transmembrane hinge, and an intracellular activation signal (usually CD3). Several generations of CAR-T cell were tested with one and or several co-stimulatory signals (e.g. CD28, CD137, OX40) to increase T cells activation and persistence after injection to the

patients. Unlike unmanipulated T cells, CAR-T cells recognize tumor cells in an antibody-dependent manner, thus with a higher affinity than TCRs and in an HLA-independent manner. In 2008, Till et al reported the first study testing CAR-T cell in hematological malignancies[42]. These CD20 CAR-T cells were used to treat patients with B-NHL (n=7). The results were disappointing, probably because of the short persistence of CARs in the body, despite repeated injections of IL-2. Since then, new generations of CAR-T cells combined with the use of lymphodepleting conditioning regimens have significantly improved these results. CARs directed against CD19 have shown dramatic activity in refractory or relapsed patient with acute lymphoid leukemia (up to 90% complete remission rate)[43,44] and NHL, explaining the current enthusiasm for these new therapies (Table 5). In August 2017, this first-in-class therapy (CTL019) was approved by the FDA for the treatment of children and young-adults with relapse or refractory B-ALL[45]. Few months later, in October 2017, KTE-C19 was also approved by the FDA for the treatment of adults with R/R DLBCL[46].

Non-Hodgkin lymphoma

In NHL, most CAR-T cells tested are directed against CD19 (Table 5). One of the first study to report the efficacy of CD19-CARs in patients with NHL or CLL was published in 2015[47]. Among the 15 patients, 6 out of 7 DLBCL patients experienced objective responses, including 4 CR, and 2 out of 2 patients with indolent lymphoma experienced an objective response, including one CR. Brudno et al reported the results of allogenic CAR-T cells in 20 patients with B cell malignancies who had relapsed after an allogenic-HSCT. Eight out of 20 patients experienced an objective response including 6 CR without induction of GVHD[48]. A recent study demonstrated an ORR of 73% (including 55% CR) among 22 patients with B-NHL (mostly DLBCL, N=19)[49]. Eleven of the 12 CR were still ongoing at the time of publication. Interestingly, the study found that high serum IL-15 levels were associated with high peak blood CAR T cell levels and remissions of lymphoma.

The 3 most advanced CAR-T cells developed for lymphoma are CTL019 (Novartis/UPenn), JCAR (Juno/MSKCC), and KTE-C19 (Kite/NCI). These CAR T cells differ in various ways (Table 6). Recently, the ZUMA-1 study evaluated the efficacy of CD19 CAR-T cells (KTE-C19, Axicabtagene Ciloleucel, Axi-Cel) in 101 patients with refractory DLBCL/PMBL (defined by the lack of response to the last line chemotherapy or relapse within a year after an auto-HSCT). According to the SCHOLAR-I study (N = 636 patients), these patients have an extremely poor prognosis following conventional chemotherapy with only 26% objective response, 7% CR and a median overall survival of 6.3 months[50]. Intermediate results of the

ZUMA-1 study were presented at ICML 2017[51] and final results were recently published[52]. This study, the largest in patient with lymphoma, is remarkable for several reasons. First, it demonstrates the feasibility of large-scale, multicenter (national and soon international), CAR-T cells trials, as 22 Centers participated in ZUMA-1. Furthermore, it demonstrates the ability to produce CAR-T cells in a timely manner (17 days average turnaround time from apheresis and delivery to clinical site) and efficiently (99% manufacturing success rate). The efficacy is remarkable in these patients known to have a very poor prognosis with 42% of patients responding at 15 months, 40% of whom remain in complete response after a median follow-up of 15.4 months, and a median overall survival not reached. The median duration of response was 11.1 months and was not reached for patients in complete response. At 6 months, 78% of patients were still alive (versus 55% in the SCHOLAR-I study). CTL019, another CD19 CAR-T cell, was also evaluated in patients with refractory DLBCL. Intermediate results from the JULIET study were presented at ICML 2017[53] and ASH 2017[54]. Analysis of 81 patients followed for at least 3 months found 53% of best objective response with 40% of complete responses. Most patients in complete response at 3 months presented ongoing response at 6 months. A third type of CD19 CAR-T cells, JCAR017, was also evaluated in NHL patients. In the TRANSCEND study, these CAR-T cells were administered with a CD4/CD8 ratio of 1:1 instead of a bulk of T cells in the two previous studies (ZUMA-1 and JULIET)[55,56]. The 3-month analysis showed an overall response of 53%, including 44% CR, among 72 evaluable patients[56]. Although, the manufacturing success was uniformly high across all three studies (99% for ZUMA-1, 94% for JULIET and 98% for TRANSCEND), the infusion rates (i.e. # infused / # leukapheresed) were significantly different (91% for ZUMA-1 (101/111), 70% for JULIET (99/141) and 77% for TRANSCEND (108/140). Thus, the characteristics of the patients infused may differ between the studies, rendering any comparison difficult.

Although these results are very encouraging, it should be noted that the efficacy of CAR-T cells in lymphoma appears to be lower than that observed in ALL for a reason that is not yet well understood (role of the microenvironment?). Moreover, these new drugs often harbor significant toxicities, including cytokine release syndromes and a neurological toxicity. In the ZUMA-1 study, almost all patients (95%) experienced grade ≥3 toxicity, mostly hematologic toxicity which was related in part to the conditioning regimen[51]. In addition, cytokine release syndromes were reported, 18% of which were grade 3. A significant proportion of patients received tocilizumab, an anti-IL6 receptor antagonist (43%) and/or systemic corticosteroids

(27%). These immunosuppressive treatments did not seem to impact the response. Neurological toxicity (mainly unspecific encephalopathies) is also frequently observed, including 13% of grade 3. These toxicities are almost always reversible without sequelae and the safety profiles appear to be comparable in the 3 studies, ZUMA-1, JULIET and TRANSCEND (Table 6).

Just like "natural" T cells, CAR T cells may be inhibited by PD1-PDL1 interaction. Thus, PD1 blockade may further enhance CAR T cells efficacy. Chong et al[57] reported the case of a patient with refractory DLBCL progressing after CD19 CAR therapy. Infusion of pembrolizumab at day + 26 after CAR therapy resulted in lymphoma regression and expansion of CAR T cells. Clinical trials combining CAR T cells and PD1 blockers are ongoing (NCT02650999 and NCT02926833). Potential combinations to further improve CAR T cells efficacy are discussed in the review by Khalil et al[58].

Finally, CAR-T cells may be effective in lymphoma patients with central nervous system involvement. A recent publication reported the case of a 68 years-old-woman presenting with refractory DLBCL associated with a brain lesion. This patient experienced a complete response with disappearance of the brain lesion following treatment with JCAR017[59].

Hodgkin lymphoma

CD30 CAR T-cells were tested in 18 patients with relapse/refractory CD30+ lymphoma (17 HL and 1 cutaneous ALCL)[60]. Seven patients experienced a partial response (39%) with a good safety (Table 5). Several other clinical trials evaluating anti-CD30 CAR T cells are ongoing.

Conclusion

CPI, TCE, and CAR-T cells represent new types of immunotherapies which offer novel perspectives for the management of patients with lymphoma who have failed conventional therapies. How these different immunotherapies will be integrated in future therapeutic strategies remains to be determined. Each of them presents specific advantages (Table 1). Furthermore, they may benefit different patients. Finally, these immunotherapies may help each other and work synergistically (e.g. CPI with TCE or CAR-T cells, Table 3 and 7). Thus, these new immunotherapies should be seen as complementary rather than competitive. Ongoing and future studies should help identify which of these therapies (or their

combination) is more likely to benefit a given patient. This is the beginning of a new and exciting era in which each patient will be offered a "personalized immunotherapy" based on the status of his tumor and immune system.

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Reference

1. Kumar, V. *et al.* Current Diagnosis and Management of Immune Related Adverse Events (irAEs) Induced by Immune Checkpoint Inhibitor Therapy. *Front. Pharmacol.* **8,** 49 (2017).

2. Roemer, M. G. M. *et al.* PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. *J. Clin. Oncol.* **34,** 2690–7 (2016).

3. Green, M. R. *et al.* Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. *Clin. Cancer Res.* **18,** 1611–8 (2012).

4. Younes, A. *et al.* Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet. Oncol.* **17,** 1283–94 (2016).

5. Liu, Y. *et al.* The mutational landscape of Hodgkin lymphoma cell lines determined by whole-exome sequencing. *Leukemia* **28,** 2248–2251 (2014).

6. Poppema, S. & Visser, L. Absence of HLA class I expression by Reed-Sternberg cells. *Am. J. Pathol.* **145,** 37–41 (1994).

7. Oudejans, J. J. *et al.* Analysis of major histocompatibility complex class I expression on Reed-Sternberg cells in relation to the cytotoxic T-cell response in Epstein-Barr virus-positive and -negative Hodgkin's disease. *Blood* **87,** 3844–51 (1996).

8. Roemer, M. G. M. *et al.* Classical Hodgkin Lymphoma with Reduced β2M/MHC Class I Expression Is Associated with Inferior Outcome Independent of 9p24.1 Status. *Cancer Immunol. Res.* **4,** 910–916 (2016).

9. Ansell, S. M. *et al.* PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. *N. Engl. J. Med.* **372,** 311–319 (2015).

10. Armand, P. *et al.* Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. *J. Clin. Oncol.* **34,** 3733–3739 (2016).

11. Engert, A. et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma after autologous transplant: full results after extended follow-up of the multicohort muticenter phase 2 CHECKMATE 205 trial. Proceedings of the 22th annual congress of the EHA. Absract S412. in (2017).

12. Chen, R. *et al.* Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. *J. Clin. Oncol.* **35,** 2125–2132 (2017).

13. A., E. *et al.* Checkmate 205: A phase 2 study of nivolumab in patients with classical hodgkin lymphoma following autologous stem cell transplantation and brentuximab vedotin. *Haematologica* **101,** 319 (2016).

14. Merryman, R. W. *et al.* Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. *Blood* **129,** 1380–1388 (2017).

15. Beköz, H. *et al.* Nivolumab for relapsed or refractory Hodgkin lymphoma: real-life experience. *Ann. Oncol.* **28,** 2496–2502 (2017).

16. Herbaux, C. *et al.* Efficacy and tolerability of nivolumab after allogeneic transplantation for relapsed Hodgkin lymphoma. *Blood* **129,** 2471–2478 (2017).

17. Haverkos, B. M. *et al.* PD-1 blockade for relapsed lymphoma post–allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood* **130,** 221–228 (2017).

18. Chen, R. *et al.* Blockade of the PD-1 checkpoint with anti-PD-L1 antobody avelumab is suficient for clinical activity in relapsed/refractory Classical Hodgkin Lymphoma (CHL). *Hematol. Oncol.* **35,** 67–67 (2017).

19. Herrera, A. F. *et al.* Interim results from a phase 1/2 study of Brentuximab Vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Hematol. Oncol.* **35,** 85–86 (2017).

20. Diefenbach, C. S. *et al.* Safety and efficacy of combination of brentuximab vedotin and nivolumab in relapsed/refractory Hodgkin Lymphoma: a Trial of the ECOG-ACRIN cancer research group (E4412). *Hematol. Oncol.* **35,** 84–85 (2017).

21. Herrera, A. F. *et al.* Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood* blood-2017-10-811224 (2017). doi:10.1182/blood-2017-10-811224

22. Ansell, S. *et al.* A Phase 1 Study of Nivolumab in Combination with Ipilimumab for Relapsed or Refractory Hematologic Malignancies (CheckMate 039). *Blood* **128,** 183 (2016).

23. Ansell, S. M. *et al.* Phase I Study of Ipilimumab, an Anti-CTLA-4 Monoclonal Antibody, in Patients with Relapsed and Refractory B-Cell Non-Hodgkin Lymphoma. *Clin. Cancer Res.* **15,** 6446–6453 (2009).

24. Bashey, A. *et al.* CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. *Blood* **113,** 1581–1588 (2009).

25. Davids, M. S. *et al.* Ipilimumab for Patients with Relapse after Allogeneic Transplantation. *N. Engl. J. Med.* **375,** 143–53 (2016).

26. Lesokhin, A. M. *et al.* Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J. Clin. Oncol.* **34,** 2698–2704 (2016).

27. Chen, B. J. *et al.* PD-L1 Expression Is Characteristic of a Subset of Aggressive B-cell Lymphomas and Virus-Associated Malignancies. *Clin. Cancer Res.* **19,** 3462–3473 (2013).

28. Chapuy, B. *et al.* Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood* **127,** 869–881 (2016).

29. Zinzani, P. L. *et al.* Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. *Blood* **130,** 267–270 (2017).

30. Zinzani, P. *et al.* Efficacy and safety of pembrolizumab in relapsed/refractory primary mediastinal large B-cell lymphoma (rrPMBCL): interim analysis of the KEYNOTE-170 phase 2 trial. *Hematol. Oncol.* **35,** 62–63 (2017).

31. Nayak, L. *et al.* PD-1 blockade with nivolumab in relapsed / refractory primary central nervous system and testicular lymphoma. *Blood* **129,** 3071–3074 (2017).

32. Ding, W. *et al.* Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood* **129,** 3419–3427 (2017).

33. Khodadoust, M. *et al.* Pembrolizumab for Treatment of Relapsed/Refractory Mycosis Fungoides and Sezary Syndrome: Clinical Efficacy in a Citn Multicenter Phase 2 Study. *Blood* **128,** 181 (2016).

34. Kwong, Y.-L. *et al.* PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood* **129,** 2437–2442 (2017).

35. Topp, M. S. *et al.* Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* **16,** 57–66 (2015).

36. Kantarjian, H. *et al.* Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* **376,** 836–847 (2017).

37. Goebeler, M.-E. *et al.* 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,** 1104–11 (2016).

38. Viardot, A. *et al.* Phase 2 study of bispecific T-cell engager (BiTE(R)) antibody blinatumomab in relapsed/refractory diffuse large B cell lymphoma. *Blood* **127,** 1410–1417 (2016).

39. Bannerji, R. *et al.* Phase 1 study of REGN1979, an Anti-CD20 x Anti-CD3 bispecific monoclonal antibody, in patients with CD20+ B-cell malignancies previously treated with CD20-directed antibody therapy. *Blood* **128,** 183 (2016).

40. Schuster, F. R. *et al.* Immunotherapy with the trifunctional anti-CD20 x anti-CD3 antibody FBTA05 (Lymphomun) in paediatric high-risk patients with recurrent CD20-positive B cell malignancies. *Br. J. Haematol.* **169,** 90–102 (2015).

41. Rothe, A. *et al.* A phase 1 study of the bispecific anti-CD30/CD16A antibody construct AFM13 in patients with relapsed or refractory Hodgkin lymphoma. *Blood* **125,** 4024–4031 (2015).

42. Till, B. G. *et al.* Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells. *Blood* **112,** 2261–2271 (2008).

43. Maude, S. L. *et al.* Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. *N. Engl. J. Med.* **371,** 1507–1517 (2014).

44. Gardner, R. A. *et al.* Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. *Blood* **129,** 3322–3331 (2017).

45. FDA - U.S. Food & Drug Administration. Press Announcements - FDA approval brings first gene therapy to the United States. (2017). at <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm574058.htm>

46. FDA - U.S. Food & Drug Administration. FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma. (2017). at <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm581216.htm>

47. Kochenderfer, J. N. *et al.* Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J. Clin. Oncol.* **33,** 540–9 (2015).

48. Brudno, J. N. *et al.* Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease. *J. Clin. Oncol.* **34,** 1112–21 (2016).

49. Kochenderfer, J. N. *et al.* Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. *J. Clin. Oncol.* **35,** 1803–1813 (2017).

50. Crump, M. *et al.* Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* **243,** blood-2017-03-769620 (2017).

51. Neelapu, S. S. *et al.* Axicabtagene ciloleucelL (AXI-CEL; KTE-C19) in patient with refractory aggressive Non-Hodgkin Lymphoma (NHL): Primary results of the pivotal trial ZUMA-1. *Hematol. Oncol.* **35,** 28–28 (2017).

52. Neelapu, S. S. *et al.* Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell

Lymphoma. *N. Engl. J. Med.* **377,** 2531–2544 (2017).

53. Schuster, S. J. *et al.* Global pivotal phase 2 trial of the CD19-targeted therapy CTL019 in adult patients with relapsed or refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)- An interim analysis. *Hematol. Oncol.* **35,** 27–27 (2017).

54. Schuster, S. J. *et al.* 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,** (2017).

55. Abramson, J. *et al.* High CR rates in Relapsed/Refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T CELL product JCAR017 (TRANSCEND NHL 001). *Hematol. Oncol.* **35,** 138–138 (2017).

56. Abramson, J. S. *et al.* 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,** (2017).

57. Chong, E. A. *et al.* PD-1 blockade modulates chimeric antigen receptor (CAR)-modified T cells: refueling the CAR. *Blood* **129,** 1039–1041 (2017).

58. Khalil, D. N., Smith, E. L., Brentjens, R. J. & Wolchok, J. D. The future of cancer treatment: Immunomodulation, CARs and combination immunotherapy. *Nature Reviews Clinical Oncology* **13,** 273–290 (2016).

59. Abramson, J. S. *et al.* Anti-CD19 CAR T Cells in CNS Diffuse Large-B-Cell Lymphoma. *N. Engl. J. Med.* **377,** 783–784 (2017).

60. Wang, C.-M. *et al.* Autologous T Cells Expressing CD30 Chimeric Antigen Receptors for Relapsed or Refractory Hodgkin Lymphoma: An Open-Label Phase I Trial. *Clin. Cancer Res.* **23,** 1156–1166 (2017).

61. Jain, N. *et al.* Nivolumab Combined with Ibrutinib for CLL and Richter Transformation: A Phase II Trial. *Blood* **128,** (2016).

62. Schuster, S. J. *et al.* Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N. Engl. J. Med.* **377,** 2545–2554 (2017).

63. Turtle, C. J. *et al.* 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,** 355ra116 (2016).

64. Wang, X. *et al.* Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL. *Blood* **127,** 2980–2990 (2016).

65. Locke, F. L. *et al.* Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Mol. Ther.* **25,** 285–295 (2017).

66. Ramos, C. A. *et al.* Clinical and immunological responses after CD30-specific chimeric antigen receptor–redirected lymphocytes. *J. Clin. Invest.* **127,** 3462–3471 (2017).

67. Frey, B. *et al.* Immunomodulation by ionizing radiation-impact for design of radio-immunotherapies and for treatment of inflammatory diseases. *Immunol. Rev.* **280,** 231–248 (2017).

68. Reits, E. A. *et al.* Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J. Exp. Med.* **203,** 1259–71 (2006).

69. Vereecque, R. *et al.* gamma-ray irradiation induces B7.1 expression in myeloid leukaemic

cells. *Br. J. Haematol.* **108,** 825–31 (2000).

70. Spisek, R. *et al.* Bortezomib enhances dendritic cell (DC)-mediated induction of immunity to human myeloma via exposure of cell surface heat shock protein 90 on dying tumor cells: therapeutic implications. *Blood* **109,** 4839–45 (2007).

71. Casares, N. *et al.* Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death. *J. Exp. Med.* **202,** 1691–701 (2005).

72. Ghiringhelli, F. *et al.* Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. *Cancer Immunol. Immunother.* **56,** 641–8 (2007).

73. Soeda, A. *et al.* Regular Dose of Gemcitabine Induces an Increase in CD14+ Monocytes and CD11c+ Dendritic Cells in Patients with Advanced Pancreatic Cancer. *Jpn. J. Clin. Oncol.* **39,** 797–806 (2009).

74. de Biasi, A. R., Villena-Vargas, J. & Adusumilli, P. S. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. *Clin. Cancer Res.* **20,** 5384–91 (2014).

75. DeNardo, D. G. *et al.* Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov.* **1,** 54–67 (2011).

76. Lim, S. H. *et al.* Effect of neoadjuvant chemoradiation on tumor-infiltrating/associated lymphocytes in locally advanced rectal cancers. *Anticancer Res.* **34,** 6505–13 (2014).

77. Lefebvre, M.-L., Krause, S. W., Salcedo, M. & Nardin, A. Ex vivo-activated human macrophages kill chronic lymphocytic leukemia cells in the presence of rituximab: mechanism of antibody-dependent cellular cytotoxicity and impact of human serum. *J. Immunother.* **29,** 388–97 (2006).

78. Zhou, X., Hu, W. & Qin, X. The role of complement in the mechanism of action of rituximab for B-cell lymphoma: implications for therapy. *Oncologist* **13,** 954–66 (2008).

79. Müller, P. *et al.* Microtubule-depolymerizing agents used in antibody-drug conjugates induce antitumor immunity by stimulation of dendritic cells. *Cancer Immunol. Res.* **2,** 741–55 (2014).

80. Buchbinder, E. I. & Desai, A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *Am. J. Clin. Oncol.* **39,** 98–106 (2016).

81. Houot, R. *et al.* Therapeutic effect of CD137 immunomodulation in lymphoma and its enhancement by Treg depletion. *Blood* **114,** 3431–8 (2009).

82. Nocentini, G., Ronchetti, S., Petrillo, M. G. & Riccardi, C. Pharmacological modulation of GITRL/GITR system: therapeutic perspectives. *Br. J. Pharmacol.* **165,** 2089–99 (2012).

83. Nguyen, L. T. & Ohashi, P. S. Clinical blockade of PD1 and LAG3--potential mechanisms of action. *Nat. Rev. Immunol.* **15,** 45–56 (2015).

84. Ellmark, P., Mangsbo, S. M., Furebring, C., Tötterman, T. H. & Norlén, P. Kick-starting the cancer-immunity cycle by targeting CD40. *Oncoimmunology* **4,** e1011484 (2015).

85. He, L.-Z. *et al.* Agonist Anti-Human CD27 Monoclonal Antibody Induces T Cell Activation and Tumor Immunity in Human CD27-Transgenic Mice. *J. Immunol.* **191,** 4174–4183 (2013).

86. Roberts, D. J. *et al.* Control of Established Melanoma by CD27 Stimulation Is Associated With Enhanced Effector Function and Persistence, and Reduced PD-1 Expression of Tumor Infiltrating CD8+ T Cells. *J. Immunother.* **33,** 769–779 (2010).

87. Thielens, A., Vivier, E. & Romagné, F. NK cell MHC class I specific receptors (KIR): from

biology to clinical intervention. *Curr. Opin. Immunol.* **24,** 239–245 (2012).

88. Chao, M. P. *et al.* Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. *Cell* **142,** 699–713 (2010).

89. Liu, X. *et al.* CD47 blockade triggers T cell–mediated destruction of immunogenic tumors. *Nat. Med.* **21,** 1209–1215 (2015).

90. Bartlett, J. B., Dredge, K. & Dalgleish, A. G. Timeline: The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat. Rev. Cancer* **4,** 314–322 (2004).

91. Galustian, C. *et al.* The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. *Cancer Immunol. Immunother.* **58,** 1033–45 (2009).

92. Munn, D. H. & Mellor, A. L. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. *J. Clin. Invest.* **117,** 1147–54 (2007).

93. Sagiv-Barfi, I., Kohrt, H. E., Burckhardt, L., Czerwinski, D. K. & Levy, R. Ibrutinib enhances the antitumor immune response induced by intratumoral injection of a TLR9 ligand in mouse lymphoma. *Blood* **125,** 2079–86 (2015).

94. Dubovsky, J. A. *et al.* Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood* **122,** 2539–49 (2013).

95. O'Donnell, J. S., Massi, D., Teng, M. W. L. & Mandala, M. PI3K-AKT-mTOR inhibition in cancer immunotherapy, redux. *Semin. Cancer Biol.* (2017). doi:10.1016/j.semcancer.2017.04.015

96. Chiappinelli, K. B. *et al.* Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses. *Cell* **162,** 974–86 (2015).

97. Cao, K. *et al.* Histone deacetylase inhibitors prevent activation-induced cell death and promote anti-tumor immunity. *Oncogene* **34,** 5960–5970 (2015).

98. West, A. C. *et al.* An intact immune system is required for the anticancer activities of histone deacetylase inhibitors. *Cancer Res.* **73,** 7265–76 (2013).

99. Peng, D. *et al.* Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy. *Nature* **527,** 249–253 (2015).

100. Zingg, D. *et al.* The Histone Methyltransferase Ezh2 Controls Mechanisms of Adaptive Resistance to Tumor Immunotherapy. *Cell Rep.* **20,** 854–867 (2017).

101. Yang, H. *et al.* STAT3 Inhibition Enhances the Therapeutic Efficacy of Immunogenic Chemotherapy by Stimulating Type 1 Interferon Production by Cancer Cells. *Cancer Res.* **75,** 3812–3822 (2015).

102. Goel, S. *et al.* CDK4/6 inhibition triggers anti-tumour immunity. *Nature* **548,** 471–475 (2017).

103. Brown, J. S., Sundar, R. & Lopez, J. Combining DNA damaging therapeutics with immunotherapy: more haste, less speed. *Nat. Publ. Gr.* (2017). doi:10.1038/bjc.2017.376

104. Kaczanowska, S., Joseph, A. M. & Davila, E. TLR agonists: our best frenemy in cancer immunotherapy. *J. Leukoc. Biol.* **93,** 847–63 (2013).

105. Rivera Vargas, T., Benoit-Lizon, I. & Apetoh, L. Rationale for stimulator of interferon genes–targeted cancer immunotherapy. *Eur. J. Cancer* **75,** 86–97 (2017).

106. Zhou, X. & Jiang, Z. STING-mediated DNA sensing in cancer immunotherapy. *Sci. China Life Sci.* **60,** 563–574 (2017).

107. Workenhe, S. T. & Mossman, K. L. Oncolytic virotherapy and immunogenic cancer cell death: sharpening the sword for improved cancer treatment strategies. *Mol. Ther.* **22,** 251–256 (2014).

108. Zhou, H. *et al.* The oncolytic peptide LTX-315 triggers immunogenic cell death. *Cell Death Dis.* **7,** e2134–e2134 (2016).

109. Sveinbjørnsson, B., Camilio, K. A., Haug, B. E. & Rekdal, Ø. LTX-315: a first-in-class oncolytic peptide that reprograms the tumor microenvironment. *Future Med. Chem.* **9,** 1339–1344 (2017).

110. Wu, J., Fu, J., Zhang, M. & Liu, D. AFM13: a first-in-class tetravalent bispecific anti-CD30/CD16A antibody for NK cell-mediated immunotherapy. *J. Hematol. Oncol.* **8,** 96 (2015).

111. Smith, E. J. *et al.* A novel, native-format bispecific antibody triggering T-cell killing of B-cells is robustly active in mouse tumor models and cynomolgus monkeys. *Sci. Rep.* **5,** 17943 (2015).

112. Cherkassky, L. *et al.* Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor-mediated inhibition. *J. Clin. Invest.* **126,** 3130–44 (2016).

113. Melero, I., Vile, R. & Colombo, M. Feeding dendritic cells with tumor antigens: self-service buffet or à la carte? *Gene Ther.* **7,** 1167–1170 (2000).

114. Melief, C. J. M., van Hall, T., Arens, R., Ossendorp, F. & van der Burg, S. H. Therapeutic cancer vaccines. *J. Clin. Invest.* **125,** 3401–3412 (2015).

115. Parker, B. S., Rautela, J. & Hertzog, P. J. Antitumour actions of interferons: implications for cancer therapy. *Nat. Rev. Cancer* **16,** 131–144 (2016).

Tables

Table 1. Comparison between new immunotherapies

	Checkpoint inhibitors (CPI)	T-Cell engager Ab (TCE)	Chimeric Ag receptor-T cells (CAR)
Type of therapy	Antibody	Antibody	Adoptive cell therapy
Mechanism of action	Block inhibitory signals on T cells	Recruit and activate T cells at the tumor site	Genetically modified T cells recognize and kill tumor cells
Requirement for tumor Ag identification	No	Yes	Yes
Specificity against tumor cells	Polyclonal	Monoclonal[1]	Monoclonal[1]
Nature of Ag targeted	Intracellular and surface	Surface	Surface
HLA-restricted recognition of Ag	Yes	No[2]	No[2]
Long lasting protection	Yes[3]	No[4]	Yes[5]
Off-the-shelf	Yes	Yes	No
Administration	Sequential	Continuous[6]	Single
Half-life	Weeks	Hours[6]	Months/Years [5]
Personalized therapy[7]	0	+	+++
Main toxicities	Immune-related adverse events (irAE)	Neurotoxicity	• Cytokine release syndrome • Neurotoxicity
FDA-approved for cancer	Anti-CTLA-4: ipilimumab Anti-PD-1: nivolumab, pembrolizumab Anti-PDL-1: atezolizumab, avelumab, durvalumab	Anti-CD3/CD19: blinatumomab	CD19 CAR-T : KTE-C19, CTL-019

[1] *Risk of escape by loss/mutation of the target*
[2] *Efficacy preserved despite loss of HLA expression*
[3] *Treatment may induce an immune memory. Thus, the efficacy may persist beyond elimination of the Ab*
[4] *Efficacy is lost when the Ab gets eliminated after a few hours/days*
[5] *CAR T cells can persist for months/years after injection*
[6] *Blinatumomab is a single-chain variable fragment (scFv) with a very short half-life (≈2h) which requires continuous infusions over several weeks. Other TCE are in development which have longer half-lives allowing discontinuous (i.e. sequential) administration.*[7] *CPI do not require Ag identification and are not restricted to a particular type of tumor or patients. TCE are restricted to tumors expressing the target (e.g. CD19). CAR T cells have to be custom-made to correspond to a given tumor (CD19 for instance) and a given patient (autologous CAR T cells). Some recent approaches are developing allogenic CAR T cells which may apply to different patients ("universal CAR T cells")*

Table 2. Main clinical results of CPIs in lymphoma

	I-O target	Treatment	Indication	Phase	Number of patients	Main results
Non-Hodgkin Lymphoma	CTLA-4	Ipilimumab	r/r LNH	I	18	ORR = 11%. CR = 6%. PR = 6%[23]
			Relapse post-alloHSCT hematological malignancies	I	29	ORR = 10%. CR = 3%. PR = 7%[24]
				I	11	7 HL: ORR = 0% 4 NHL: ORR = 25%. PR = 25%[25]
	PD-1	Pembrolizumab	r/r PMBL	I	17	ORR = 41%. CR = 12%. PR = 29%[29]
				II	29	ORR = 41%. CR = 14%. PR = 28%[30]
			r/r T/NK NHL		7	ORR = 100%. CR = 71%. PR = 29%[34]
			r/r MF/SS	I	24	ORR = 38%. CR = 4%. PR = 33%[33]
			r/r CLL/RS	II	25	16 CLL : ORR = 0% 9 RS : ORR = 44%. CR = 11%[32]
		Nivolumab	r/r NHL	I	23	11 DLBCL: ORR = 36%. CR = 18%. PR = 18% 2 PMBL: ORR = 0%. SD = 100% 10 FL: ORR = 40%. CR = 10%. PR = 30%[26]
			r/r PCNSL		5	ORR = 100%. CR = 80%. PR = 20%[31]
		Nivolumab + ibrutinib	r/r CLL/RS	II	8	4 CLL: ORR = 75%. CR = 0%. PR = 75% 4 RS: ORR = 50%. CR = 25%. PR = 25%[61]
	PD-1 + CTLA-4	Nivolumab + ipilimumab	DLBCL/FL	I	15	ORR = 13%. CR = 0%. PR = 13%, SD = 7%[22]
Hodgkin Lymphoma	PD-1	Nivolumab	r/r HL	I	23	ORR = 78%. CR = 17%[9]
				II	243	Cohort 1 (N=63): ORR = 65%. CR = 29% Cohort 2 (N=80): ORR = 68%. CR= 13% Cohort 3 (N=100): ORR = 73%. CR= 12%[11]
			Relapse post-alloHSCT HL		20	ORR = 95%. CR = 42%. PR = 52%[16]
					31	ORR = 77%. CR = 50%. PR = 27%[17]
		Pembrolizumab	r/r HL	I	31	ORR = 65%. CR = 16%. PR = 48%[10]
				II	210	Cohort 1 (N=69): ORR = 74%. CR = 22% Cohort 2 (N=81): ORR = 64%. CR = 25% Cohort 3 (N=60): ORR = 70%. CR = 20%[12]
		Nivolumab + BV	r/r HL	I	18	ORR = 89%, CR = 61%[20]
				I/II	62	ORR = 82%. CR = 61%[21]
	PD-L1	Avelumab	r/r HL	I	31	ORR = 42%, CR = 16%[18]
	PD-1 + CTLA-4	Nivolumab + ipilimumab	r/r HL	I	31	ORR = 74%. CR = 19%[22]

HSCT, Hematological Stem-Cell Transplantation; NHL, Non-Hodgkin Lymphoma ; CLL, Chronic Lymphoid Leukemia ; DLBCL, Diffuse Large B Cell Lymphoma ; PMBL, Primary Mediastinal B-cell Lymphoma ; MF/SS, mycosis fungoid/Sezary Syndrome ; FL, Follicular Lymphoma ; PCNSL, Primary Central Nervous System Lymphoma; RS, Richter Syndrome; pts, Patients ; ORR, Overall Response Rate ; CR, Complete Response ; PR, Partial Response ; SD, Stable Disease ; HL, Hodgkin Lymphoma ; HSCT, Hematopoietic Stem Cell Transplantation, BV, Brentuximab Vedotin.

Table 3. Ongoing clinical trials testing combinations with anti-PD1/PDL1 Abs in lymphoma[1]

Anti-PD-1/PD-L1 combination			Hodgkin lymphoma	Non-Hodgkin lymphoma
Radiotherapy			NCT03179917	NCT02677155
Chemotherapy		ABVD	NCT03033914	
		AVD	NCT03004833	
		ICE	NCT03077828 NCT03016871	
		R-CHOP		NCT02541565
		R-Bendamustine		NCT02733042
		CHOP/Bendamustine		NCT02596971 NCT02541565
Anti-tumor antibodies	Anti-CD20	Rituximab		NCT02677155 NCT02596971 NCT02446457
		Obinutuzumab		NCT02220842 NCT02596971 (+chemotherapy) NCT02631577 (+lenalidomide)
	Anti-CD19	MEDI-551		NCT02271945
Antibody-drug conjugate	Anti-CD30	Brentuximab Vedotin	NCT02684292 NCT02572167 NCT02581631 NCT03057795 NCT02758717 NCT02927769 NCT03138499 NCT01716806	NCT02581631
	Anti-CD79b	Polatuzumab Vedotin		NCT02729896 (+obinutuzumab)
Immuno-oncology agents	Anti-CTLA4	Ipilimumab	NCT02304458 NCT01896999 (+ Bv)	NCT02304458 NCT02681302
		Tremelimumab		NCT02549651
	Anti-CD137	Urelumab		NCT02253992
		Utomilumab		NCT02951156
	Anti-GITR	GWN323		NCT02740270

	Anti-LAG3	BMS-986016		NCT02061761
		BI 754111		NCT03156114
	Anti-CD40	SEA-CD40		NCT02376699
	Anti-CD27	Varlilumab		NCT03038672
	Anti-KIR	Lirilumab	NCT01592370	NCT01592370
	Anti-CD47	ALX148		NCT03013218
		TTI-621		NCT02663518
IMID		Lenalidomide	NCT03015896 NCT02875067 NCT02733042	NCT03015896 NCT01953692 NCT03011814 NCT02733042 (+rituximab) NCT03054532 NCT03003520 (+RCHOP)
IDO inhibitor		Epacadostat	NCT02327078	NCT02327078 NCT02178722
BCR inhibitor	BTK	Ibrutinib	NCT02940301	NCT02950220 NCT02329847 NCT03153202 NCT02401048 NCT03204188 (+fludarabine) NCT02846623 (+obinutuzumab)
		Acalabrutinib	NCT02362035	NCT02362035
		BGB-3111		NCT02795182
	PI3K	Idelalisib		NCT02332980
Epigenetic therapy	Hypomethylating agents	Azacitidine		NCT02951156
		Decitabine	NCT02961101	NCT02961101
	HDAC	Vorinostat	NCT03150329	NCT03150329
		Entinostat		NCT03179930
		Romidepsin		NCT03161223 (+/-azacitidine)
	EZH2	Tazemetostat		NCT02220842
	Multiple epi-enzymes	RRx-001		NCT02518958
STAT3 inhibitor		AZD9150		NCT02549651

CDK inhibitor		Dinaciclib		NCT02684617
PARP inhibitor		Veliparib		NCT03061188
TLR agonist	TLR3	Poly ICLC		NCT02643303 (+anti-CTLA-4 +anti-PDL1)
	TLR4	G100		NCT02501473
STING agonist		MK-1454		NCT03010176
		MIW815		NCT03172936
Oncolytic virus		T-Vec		NCT02978625
Oncolytic peptide (intratumoral)		LTX-315		NCT01986426
Bispecific antibodies	Anti-CD30/CD16A	AFM 13	NCT02665650	
	Anti-CD20/CD3	REGN1979		NCT02651662
Cell therapy	CAR-T cells	KTE-C19		NCT02926833
		JCAR014		NCT02706405
	EBV specific T-cells	EB-VST Cells		NCT02973113
	Autologous dendritic cells (intratumoral)			NCT02677155 NCT03035331
Vaccine therapy				NCT03121677
Interferon γ1b				NCT03063632
Sequential combination of immunotherapy				NCT03169790

[1] *www.clinicaltrials.gov. accessed on July 2017*

Table 4. Main clinical results and selected ongoing trials of TCE in lymphoma

	Treatment	Target	Indication	Phase	Number of patients	Main results
Non-Hodgkin Lymphoma	Blinatumomab (BiTE)	CD3/CD19	r/r NHL	I	76	Target dose (n=35): ORR 69% DLBCL (n= 11) : ORR 55%[37]
				II/III	Ongoing (NCT02910063) Blinatumomab vs investigator's choice	
			r/r DLBCL	II	21	ORR 43%, CR 19% Median DOR = 11.6 months[38]
	Blinatumomab +lenalidomide	CD3/CD19	Relapse NHL	I	Ongoing (NCT02568553)	
	REGN1979 (BiTE)	CD3/CD20	NHL/CLL	I	20	ORR 20%[39]
	FBTA05 (triAbs)	CD20/CD3	B hematological malignancies	I	10	ORR 90%. CR 50%[40]
			Relapse post allo-HSCT NHL	I	Ongoing (NCT01138579)	
HL	AFM13 (TandAb)	CD30/CD16	r/r HL	I	26	ORR 23%[41]
				II	Ongoing (NCT02321592)	

HSCT, Hematological Stem-Cell Transplantation; NHL, Non-Hodgkin Lymphoma ; HL, Hodgkin Lymphoma ; CLL, Chronic Lymphoid Leukemia; BiTE, Bispecific T-cell Engager ; DLBCL, Diffuse Large B Cell Lymphoma ; pts, patients ; ORR, Overall Response Rate ; CR, complete response

Table 5. Main clinical results of CAR-T cells in lymphoma

	Target	Indication	Phase	Population		Main results *(infused population)*
				Enrolled	Infused	
Non-Hodgkin Lymphoma	CD19	r/r NHL	I	Unknown	15	ORR = 80%. CR = 53%. PR = 27%[47]
			I	38	28	ORR = 64 %. CR = 57%. PR = 7%[62]
			I	37	32	ORR = 50%. CR = 8%. PR = 42% in Cy group ORR = 72% CR = 40%. PR = 22% in Flu/Cy group[63]
			I	Unknown	22	ORR = 73%. CR = 55%. PR = 18%[49]
			II	147	99	JULIET trial (CTL019) Primary analysis on 81 patients: ORR = 53%. CR = 40%[54]
			II	111	101	ZUMA-I trial (KTE-C19) ORR = 82%. CR = 54%. PR = 28%[52]
			II	140	108	TRANSCEND trial (JCAR017) Full population N = 91:ORR = 74%. CR = 52%[55,56]
		r/r post auto-HSCT NHL	I	13	8	ORR = 88%. CR = 63%. PR = 25% [64]
			I	10	8	ORR = 100%. CR = 100%[64]
		Relapse post allo-HSCT	I	Unknown	20	Allo-CAR T-cells. No GVHD 1 CR among 5 DLBCL[48]
		r/r DLBCL	I	9	7	ORR = 71%. CR = 57%. PR = 14%[65]
HL	CD30	r/r HL	I	18	9	7 HL: ORR = 29%. CR = 29%[66]
			I	18	18	6 PR. 6 SD[60]

NHL, Non-Hodgkin Lymphoma ; HL, Hodgkin Lymphoma ; DLBCL, Diffuse Large B Cell Lymphoma ; pts, patients ; ORR, Overall Response Rate ; CR, Complete Response ; PR, Partial Response ; SD, Stable Disease ; HSCT, Hematopoietic Stem Cell Transplantation ; Cy, Cyclophosphamide ; Flu, Fludarabine ; GVHD, Graft versus Host Disease

Table 6. Characteristics of the main CAR T-cells tested in lymphoma[1]

	KTE-C19 (Axi-Cel)[51,52]	JCAR017[55,56]	CTL-019[53,62,54]
Univ/Pharma	NCI/Kite	MSKCC/Juno	UPenn/Novartis
Target	CD19	CD19	CD19
Costimulatory signal	CD28	4-1BB	4-1BB
Main trial in lymphoma	ZUMA-1 (NCT02348216)	TRANSCEND NHL 001 (NCT02631044)	JULIET (NCT02445248)
N (enrolled)	111	140	147
Patients/disease	Refractory DLBCL/TFL/PMBL	R/R DLBCL, TFL, FL3B, PMBL	R/R DLBCL
Bridging therapy	None	Allowed	Allowed (90%)
Restaging before conditioning	No	Yes	Yes
Conditioning regimen	Cy 500 mg/m^2 + Flu 30 mg/m^2 x 3d	Cy 300 mg/m^2 + Flu 30 mg/m^2 x 3d	Cy 250 mg/m^2 + Flu 25 mg/m^2 x 3d Or Bendamustine 90 mg/m^2 x 2d
T cells	Bulk T cells	CD4/CD8 subsets	Bulk T cells
Manufacturing success rate	99%	98%	94%
Patients infused (% among enrolled)	101 (91%)	108 (77%)	99 (67%)
Time from apheresis to delivery	17 days	Unknown	39 days
Non-hematological toxicity (grade ≥3)	• CRS: 13% • Neurotoxicity: 28%	• CRS: 1% • Neurotoxicity: 12%	• CRS: 23% • Neurotoxicity: 12%
Grade 5 toxicity (pts)	3	1	0
Efficacy	• Best ORR = 82% • Best CR = 54% • CR: 40% @ 15 months	• Best ORR = 74% • Best CR = 52% • CR: 31% @ 6 months	• Best ORR = 53% • Best CR = 40% • CR: 30% @ 6 months

[1] *Preliminary results, not meant to be comparative*
DLBCL, Diffuse Large B Cell Lymphoma; TFL, Transformed Follicular Lymphoma; FL3B, Follicular Lymphoma grade 3B; PMBL, Primary Mediastinal B lymphoma; BOR, Best Overall Response; ORR, Overall Response Rate ; CR, Complete Response ; CRS, Cytokine Release Syndrome; Cy, Cyclophosphamide; Flu, Fludarabine; d, day ; DOR, Duration Of Response ; mPFS, median Progression Free Survival.

Table 7. Immunological effects of anticancer treatments

Therapy		Immunological effect
Radiotherapy		• Induces release and presentation of tumor Ag through ICD[67] • Enhances tumor Ag presentation (induces MHC-I expression by tumor cells)[68] • Induces expression of adhesion and costimulatory molecules at the surface of tumor cells[69]
Chemotherapy		Highly variable from one chemo to another: • Promotes ICD (e.g blemomycin, bortezomib, doxorubicin)[70,71] • Depletes circulating immunosuppressive cells: MDSC, M2 macrophages, Treg cells (e.g cyclophosphamide)[72] • Increases circulating APC (e.g gemcitabine)[73] • Enhances MHC-I expression (e.g cisplatin)[74] • Facilitates tumor infiltration by immune cells (e.g paclitaxel, 5-FU)[75,76]
Anti-tumor antibodies	Anti-CD20 Anti-CD19	• Enhance ADCC and CDC[77,78]
Antibody-drug conjugates	Anti-CD30 Anti-CD79b	• Induce release of tumor Ag • Stimulate DC[79]
Immuno-oncology agents	Anti-CTLA4	• Enhances differentiation of naïve T cells [80]
	Anti-CD137	• Activates T and NK cells[81]
	Anti-GITR	• Stimulates T effector cells and inhibits Treg activity[82]
	Anti-LAG3	• Reverses T cell exhaustion[83]
	Anti-CD40	• Activates T cells, B cells, DC and macrophages[84]
	Anti-CD27	• Activates T effector cells[85,86]
	Anti-KIR	• Reverses NK cell inhibition[87]
	Anti-CD47	• Restores DC and macrophage-mediated phagocytosis[88] • Triggers T cells-mediated cytotoxicity[89]
IMIDs		• Increase T cell function and stimulate NK cell cytotoxicity[90] • Suppress Treg function and prolifération[91]
IDO inhibitors		• Restore T cell function and decrease Treg cells[92]
BCR inhibitors	BTK inhibitors	• Promote ICD[93] • Induce switch of T cells from Th2 to Th1[94]
	PI3K inhibitors	• Enhance CD8 T cell infiltration within the tumor[95] • Inhibit Treg function and infiltration in tumors and reduce myeloid cell infiltration and differentiation[95]
Epigenetic agents	Hypomethylating agents	• Enhance Ag presentation and trigger type-I IFN responses[96]
	HDAC inhibitors	• Prevent upregulation of Fas-L on TILs[97] • Promote expansion of IFNγ-producing T-cells[98]
	EZH2 inhibitors	• Increase Th1-chemokines and T-cell infiltration[99,100]
STAT3 inhibitors		• Recruit immune effector cells into the tumor bed and improve immunosurveillance[101]
CDK inhibitors		• Enhance tumor antigen presentation at tumor cell surface[102] • Suppress Treg proliferation[102]
PARP inhibitors		• Induces DNA damaging and expansion of the neoantigen repertoire and so promote ICD[103]
TLR agonists	TLR3 TLR4	• Stimulate both innate and adaptive immunity, including DC[104]
STING agonists		• Stimulate innate immunity through type I IFN[105] • Enhance DC cross-presentation activity and consequently activation of tumor-antigen specific TCD8 cells[105,106]
Oncolytic virus		• Induce ICD[107]
Oncolytic peptides (intratumoral)		• Induce ICD[108] • Recruit intratumoral CD8 T cells and decrease Treg and MDSC[109]

Bispecific antibodies	Anti-CD30/CD16A	• Recruit and activate NK cells into the tumor[110]
	Anti-CD20/CD3	• Recruit and activate T cells into the tumor[111]
Cell therapy	CAR-T cells	• PD1/PDL1 axis blockade may enhance the efficacy of CAR-T cells[112]
	EBV specific T-cells	• EBV-associated malignancies frequently express PD-L1[27]
	Autologous dendritic cells (intratumoral)	• Enhance Ag presentation to T-cells[113]
Vaccines		• Prime new antitumor T-cell responses[114]
Interferon γ1b		• Activates T, NK and DC[115] • Inhibits Treg, MDSC and tumor-associated macrophages[115]

ADCC, Antibody-Dependent Cellular Cytotoxicity; Ag, Antigen; APC, Antigen Presenting Cells; CDC, Complement-Dependent Cytotoxicity; DC, Dendritic Cells, ICD, Immunogenic cell death (i.e that enhances immunological reaction against tumor cells); MDSC, Myeloid-derived Suppressive Cells, MHC, Major Histocompatibility Complex; NK, Natural Killer; TIL, Tumor Infiltrating Lymphocytes