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► **To cite this version:**

G. Manson, R. Houot. Next generation immunotherapies for lymphoma: one foot in the future. *Annals of Oncology*, 2018, 29 (3), pp.588-601. 10.1093/annonc/mdy032 . hal-01831048

HAL Id: hal-01831048

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-01831048>

Submitted on 5 Jul 2018

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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 HL². 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 LMP1³. 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 patients⁴. 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 $\beta 2$ microglobulin gene⁵) and/or class II HLA, theoretically compromising their recognition by T cells⁶⁻⁸.

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 BV⁴. 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 fatal¹⁴. 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 died¹⁵. 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 short half-life (6 days vs \approx 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 responses¹⁸. 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 published²¹. In these studies, complete response rates were particularly high (61 and 63%, respectively). Another study (CheckMate 039) tested the combination of nivolumab and ipilimumab²². 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 allogeneic-HSCT. Patients received one injection of ipilimumab at a dose of 0.1 to 3 mg/kg²⁴. 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-HSCT²⁵. 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 1 T-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 DLBCL²⁶. 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 PDL1²⁷. 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 DLBCL²⁸. KEYNOTE-013 (NCT01953692) evaluated the efficacy of pembrolizumab (anti-PD1) in PMBL²⁹. 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 (\approx 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 CR³⁴.

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-NHL³⁷. 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 DLBCL³⁸. 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 ongoing³⁹. 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 CR⁴⁰.

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 lymphoma⁴¹. 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 malignancies⁴². 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-ALL⁴⁵. Few months later, in October 2017, KTE-C19 was also approved by the FDA for the treatment of adults with R/R DLBCL⁴⁶.

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 2015⁴⁷. 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 GVHD⁴⁸. 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 months⁵⁰. Intermediate results of the

ZUMA-1 study were presented at ICML 2017⁵¹ and final results were recently published⁵². 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 2017⁵³ and ASH 2017⁵⁴. 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 patients⁵⁶. 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 regimen⁵¹. 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 al⁵⁷ 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 al⁵⁸.

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 JCAR017⁵⁹.

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.

Funding

No funders to report

Author Disclosures

GM and RH have nothing to disclose.

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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	<ul style="list-style-type: none"> • 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 ($\approx 2h$) 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	I	29	ORR = 10%. CR = 3%. PR = 7% ²⁴	
			hematological malignancies	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	
					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 lymphoma¹

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)
		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		Dinaciclub		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)			
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 (<i>infused population</i>)
				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

1 **Table 6. Characteristics of the main CAR T-cells tested in lymphoma¹**

	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)	<ul style="list-style-type: none"> CRS: 13% Neurotoxicity: 28% 	<ul style="list-style-type: none"> CRS: 1% Neurotoxicity: 12% 	<ul style="list-style-type: none"> CRS: 23% Neurotoxicity: 12%
Grade 5 toxicity (pts)	3	1	0
Efficacy	<ul style="list-style-type: none"> Best ORR = 82% Best CR = 54% CR: 40% @ 15 months 	<ul style="list-style-type: none"> Best ORR = 74% Best CR = 52% CR: 31% @ 6 months 	<ul style="list-style-type: none"> 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		<ul style="list-style-type: none"> Induces release and presentation of tumor Ag through ICD⁶⁷ Enhances tumor Ag presentation (induces MHC-I expression by tumor cells)⁶⁸ Induces expression of adhesion and costimulatory molecules at the surface of tumor cells⁶⁹
Chemotherapy		<p>Highly variable from one chemo to another:</p> <ul style="list-style-type: none"> Promotes ICD (e.g bleomycin, 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	<ul style="list-style-type: none"> Enhance ADCC and CDC^{77,78}
	Anti-CD19	
Antibody-drug conjugates	Anti-CD30	<ul style="list-style-type: none"> Induce release of tumor Ag Stimulate DC⁷⁹
	Anti-CD79b	
Immuno-oncology agents	Anti-CTLA4	<ul style="list-style-type: none"> Enhances differentiation of naïve T cells⁸⁰
	Anti-CD137	<ul style="list-style-type: none"> Activates T and NK cells⁸¹
	Anti-GITR	<ul style="list-style-type: none"> Stimulates T effector cells and inhibits Treg activity⁸²
	Anti-LAG3	<ul style="list-style-type: none"> Reverses T cell exhaustion⁸³
	Anti-CD40	<ul style="list-style-type: none"> Activates T cells, B cells, DC and macrophages⁸⁴
	Anti-CD27	<ul style="list-style-type: none"> Activates T effector cells^{85,86}
	Anti-KIR	<ul style="list-style-type: none"> Reverses NK cell inhibition⁸⁷
	Anti-CD47	<ul style="list-style-type: none"> Restores DC and macrophage-mediated phagocytosis⁸⁸ Triggers T cells-mediated cytotoxicity⁸⁹
IMiDs		<ul style="list-style-type: none"> Increase T cell function and stimulate NK cell cytotoxicity⁹⁰ Suppress Treg function and proliferation⁹¹
IDO inhibitors		<ul style="list-style-type: none"> Restore T cell function and decrease Treg cells⁹²
BCR inhibitors	BTK inhibitors	<ul style="list-style-type: none"> Promote ICD⁹³ Induce switch of T cells from Th2 to Th1⁹⁴
	PI3K inhibitors	
Epigenetic agents	Hypomethylating agents	<ul style="list-style-type: none"> Enhance Ag presentation and trigger type-I IFN responses⁹⁶
	HDAC inhibitors	<ul style="list-style-type: none"> Prevent upregulation of Fas-L on TILs⁹⁷ Promote expansion of IFNγ-producing T-cells⁹⁸
	EZH2 inhibitors	<ul style="list-style-type: none"> Increase Th1-chemokines and T-cell infiltration^{99,100}
STAT3 inhibitors		<ul style="list-style-type: none"> Recruit immune effector cells into the tumor bed and improve immunosurveillance¹⁰¹
CDK inhibitors		<ul style="list-style-type: none"> Enhance tumor antigen presentation at tumor cell surface¹⁰² Suppress Treg proliferation¹⁰²
PARP inhibitors		<ul style="list-style-type: none"> Induces DNA damaging and expansion of the neoantigen repertoire and so promote ICD¹⁰³
TLR agonists	TLR3	<ul style="list-style-type: none"> Stimulate both innate and adaptive immunity, including DC¹⁰⁴
	TLR4	
STING agonists		<ul style="list-style-type: none"> Stimulate innate immunity through type I IFN¹⁰⁵ Enhance DC cross-presentation activity and consequently activation of tumor-antigen specific TCD8 cells^{105,106}
Oncolytic virus		<ul style="list-style-type: none"> Induce ICD¹⁰⁷
Oncolytic peptides (intratumoral)		<ul style="list-style-type: none"> Induce ICD¹⁰⁸ Recruit intratumoral CD8 T cells and decrease Treg and MDSC¹⁰⁹

Bispecific antibodies	Anti-CD30/CD16A	<ul style="list-style-type: none"> Recruit and activate NK cells into the tumor¹¹⁰
	Anti-CD20/CD3	<ul style="list-style-type: none"> Recruit and activate T cells into the tumor¹¹¹
Cell therapy	CAR-T cells	<ul style="list-style-type: none"> PD1/PDL1 axis blockade may enhance the efficacy of CAR-T cells¹¹²
	EBV specific T-cells	<ul style="list-style-type: none"> EBV-associated malignancies frequently express PD-L1²⁷
	Autologous dendritic cells (intratumoral)	<ul style="list-style-type: none"> Enhance Ag presentation to T-cells¹¹³
Vaccines		<ul style="list-style-type: none"> Prime new antitumor T-cell responses¹¹⁴
Interferon γ1b		<ul style="list-style-type: none"> Activates T, NK and DC¹¹⁵ Inhibits Treg, MDSC and tumor-associated macrophages¹¹⁵

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