Review

Overcoming the Hurdles of Autologous T-Cell-Based Therapies in B-Cell Non-Hodgkin Lymphoma

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Received: 25 November 2020; Accepted: 16 December 2020; Published: 18 December 2020

Simple Summary: The activity of novel therapies that utilize patient’s own T-cells to induce remission of B-cell non-Hodgkin lymphoma (B-NHL), including chronic lymphocytic leukemia (CLL), is still suboptimal. In this review, we summarize the clinical efficacy of T-cell-based therapies in B-NHL and provide a biologic rationale for the observed (lack of) responses. We describe and compare the acquired T-cell dysfunctions that occur in the different subtypes of B-NHL. Furthermore, we discuss new insights that could enhance the efficacy of T-cell-based therapies for B-NHL and CLL.

Abstract: The next frontier towards a cure for B-cell non-Hodgkin lymphomas (B-NHL) is autologous cellular immunotherapy such as immune checkpoint blockade (ICB), bispecific antibodies (BsAbs) and chimeric antigen receptor (CAR) T-cells. While highly successful in various solid malignancies and in aggressive B-cell leukemia, this clinical success is often not matched in B-NHL. T-cell subset skewing, exhaustion, expansion of regulatory T-cell subsets, or other yet to be defined mechanisms may underlie the lack of efficacy of these treatment modalities. In this review, a systematic overview of results from clinical trials is given and is accompanied by reported data on T-cell dysfunction. From these results, we distill the underlying pathways that might be responsible for the observed differences in clinical responses towards autologous T-cell-based cellular immunotherapy modalities between diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). By integration of the clinical and biological findings, we postulate strategies that might enhance the efficacy of autologous-based cellular immunotherapy for the treatment of B-NHL.

Keywords: immunotherapy; B-NHL; CLL; CAR T-cells; immune checkpoint blockade; bispecific antibodies; T-cell dysfunction

1. Introduction

B-cell non-Hodgkin lymphomas (B-NHL) arise during different stages of B-cell development, which is reflected by differences in biological and clinical characteristics. This also explains their distinct sensitivity to therapeutic modalities. Current treatment of B-NHL includes DNA crosslinking agents such
as cyclophosphamide, bendamustine, and purine analogs such as fludarabine in combination with CD20 targeting antibodies. In more aggressive tumor types, inhibitors of DNA synthesis such as doxorubicin are added. Our increased understanding of oncogenesis and the relevance of crosstalk between immune cells and cancer cells in the tumor microenvironment (TME) has led to the development of targeted therapies in B-NHL, such as inhibitors of the B-cell receptor signaling pathway, and inhibitors of apoptosis regulating proteins such as the Bcl-2 binding drug venetoclax [1,2]. Furthermore, the development of antibody drug conjugates, such as polatuzumab vedotin (targeting CD79b) or brentuximab vedotin (targeting CD30), has resulted in an increased armamentarium of effective drugs with acceptable toxicity [3–5]. These agents are highly active either as a single agent or in combinations, but thus far are not curative, and resistance towards these agents will ultimately develop [6,7]. The next therapeutic frontier in B-NHL is autologous T-cell-based therapy, which includes immune checkpoint blockade (ICB), bispecific antibodies (BsAbs), and chimeric antigen receptor (CAR) T-cell therapy.

ICB reverses inhibitory interactions between the T-cell and cancer cell, thereby improving cytotoxicity of tumor recognizing T-cells and inducing cancer cell lysis. Within the tumor microenvironment, chronic stimulation of tumor infiltrating lymphocytes (TILs) leads to T-cell exhaustion, which hampers proper anti-tumor responses. Blocking of inhibitory receptors, such as programmed death-1 (PD-1) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), on T-cells, or their ligands on tumor or adjacent T-cells, potentiates anti-tumor responses. Investigations of these antibodies in hematological malignancies were prompted by the success of ICB in solid tumors such as melanoma and non-small cell lung cancer [8,9] and led to impressive results in Hodgkin lymphoma (HL) [10].

In contrast to ICB, BsAbs induce tumor cell killing without the need for specific tumor cell recognition by autologous T-cells. BsAbs tether T-cells and cancer cells via CD3 on T-cells and a tumor-associated target antigen on cancer cells resulting in direct tumor cell killing. Blinatumumab was the first Food and Drug Administration (FDA)-approved CD3xCD19 bispecific T-cell engager (BiTE). This BsAb is currently only approved for relapsed/refractory acute lymphoblastic leukemia (ALL), in which trials have shown complete remission (CR) rates of around 33% [11,12].

Similar to BsAbs, CAR T-cells act through direct recognition of cancer cells. T-cells acquire CARs through retroviral or lentiviral vectors, which requires ex vivo transduction, activation, and expansion. First generation CARs consisted of an antigen binding moiety (ScFv) covalently linked to CD3 zeta, allowing tumor antigen recognition and subsequent T-cell activation [13,14]. Second generation CARs contain an additional (costimulatory) CD28 or CD137 (4-1BB) intracellular domain, which greatly enhances CAR T-cell function [15–17]. High efficacy of CAR T-cell therapy was seen in clinical trials in ALL, in which 90% of the patients achieved CR [18,19]. Since then, CAR T-cell therapy has been translated to other types of hematologic malignancies including B-NHL.

Responses to aforementioned immune therapies are still suboptimal in B-NHL, including chronic lymphocytic leukemia (CLL). By exploring clinical data and connecting them to ex vivo and in vitro observations on T-cell (dys)function, we propose underlying mechanisms of treatment failure for the most common types of B-NHL, including diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). These data are integrated in order to suggest possible solutions to the current hurdles of autologous-based T-cell therapies in B-NHL.

2. Clinical Data

2.1. Immune Checkpoint Blockade

Although response rates were modest in early trials, patients that responded to ICB were reported to be in remission for over a year [20–22]. This prompted further investigation of ICB in B-NHL (Table 1). Studies using ipilimumab (anti-CTLA-4) or pembrolizumab (anti-PD-1) showed overall response rates (ORR) between 0–11% in B-NHL [23–25]. Whereas CLL patients showed no response upon treatment with pembrolizumab, four of 9 (44%) CLL, patients with Richter’s transformation
(RT) had a response [25]. Initially, nivolumab (anti-PD-1) appeared to be more promising with an ORR of 36% and 40% for DLBCL and FL, respectively [26]. However, these initial high responses could not be confirmed in a large follow-up trial, where DLBCL patients were subdivided based on their ineligibility for autologous hematopoietic stem cell therapy (auto-HSCT) or having relapsed after auto-HSCT [27]. The 87 patients included in the auto-HSCT failed group had an ORR of 10%, while the ORR in the auto-HSCT ineligible group \((n = 34)\) was only 3% [27]. Primary mediastinal large B-cell lymphoma (PMBCL) does respond exceptionally well to ICB compared to the others B-NHL subtypes with an ORR of 48% (CR 33%) and a median duration of response (DOR) was not reached at a median follow-up time of 29 months [28].

These trials indicate that ICB monotherapy is not sufficient to elicit significant responses in B-NHL. Therefore, research has focused on combining ICB antibodies or adding other treatment modalities to enhance efficacy. Unfortunately, combining ipilimumab and nivolumab in B-NHL patients, FL or DLBCL, resulted in a modest partial response (PR) of three out of 15 patients (ORR 20%) [29]. In contrast, the combination of pembrolizumab (anti-PD-1) with rituximab greatly improved clinical outcomes in relapsed FL compared to ICB monotherapy (ORRs between 64 and 66%) [30,31]. It remains to be elucidated whether ICB significantly improves the activity of rituximab-based therapy, since single agent rituximab for FL results in ORRs between 40% and 72% [32–34]. The combination of the anti-CD20 monoclonal obinutuzumab with atezolizumab (anti-programmed death-ligand 1, PD-L1) resulted in an ORR of 57% in 26 FL patients [35]. Addition of bendamustine to a combination of obinutuzumab and atezolizumab further increased the response rate in previously untreated FL. Twelve out of 15 patients showed a response (ORR 80%), of which 10 patients had CR [36]. Even though in FL the combination of obinutuzumab and atezolizumab seems promising, in 23 DLBCL patients the ORR was only 16% [35]. However, the combination of atezolizumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) led to responses in 35 out of 40 patients (ORR 88%), with 31 obtaining CR, and therefore might be favorable compared to R-CHOP alone [37].

Combinations of ICB and lenalidomide have also been studied. Preliminary data from a phase I trial combining nivolumab with lenalidomide in 10 B-cell lymphoma patients (including DLBCL, HL, high-grade B-cell lymphoma and lymphoplasmacytic lymphoma) showed an ORR of 30% [38]. Another study tested durvalumab (anti-PD-L1) as monotherapy, or with addition of lenalidomide with or without rituximab [39]. The arm investigating durvalumab and lenalidomide was prematurely closed due to (expected) toxicity of this combination [39]. In this arm, four out of five (80%) of FL patients and two out of seven (29%) DLBCL patients showed a response upon treatment with ICB and lenalidomide, while durvalumab monotherapy did not lead to responses in both malignancies [39]. Ipilimumab and lenalidomide were also administered to a small number of patients with high-risk DLBCL, CLL, FL or MCL [40]. In seven patients that were stratified as high-risk disease after autologous stem cell transplantation (SCT), both ORR and CR rate were 86%, while the ORR was 70% in the 10 patients that relapsed following allogeneic SCT, with a CR rate of 40% [40]. These data suggest a possible benefit of lenalidomide and ipilimumab in the post-SCT setting.

The combination of nivolumab with the Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib was tested in a large phase I/II study. ORR rates in CLL/small lymphocytic leukemia (SLL) (36 patients), CLL with RT (20 patients), FL (40 patients) and DLBCL (45 patients) were 61%, 65%, 33% and 36%, respectively [41]. Except for the CLL with RT group, the ORR of the other groups were comparable to ibrutinib monotherapy [26,42–44]. These results were similar to a more recent trial in which ibrutinib was combined with durvalumab, which yielded responses in 15 out of 59 patients with FL or DLBCL (ORR 25%) [45].

Again, relatively high response rates are seen in PBMCL patients treated with a combination of ICB (nivolumab) with the anti-CD30 antibody-drug conjugate brentuximab vedotin (ORR of 73%) with CR in 11 patients (35%) [46].
Table 1. Reported studies of immune checkpoint blockade in B-cell non-Hodgkin lymphoma (B-NHL).

| Study                        | Treatment                         | Phase | Disease  | N  | CR | ORR    | Trial ID (NCT)   |
|------------------------------|-----------------------------------|-------|----------|----|----|--------|------------------|
| O'Mahony et al., 2007 [20]   | Ipilimumab                        | II    | FL       | 2  | 0/2 (0%) | 1/2 (50%)      | N/A              |
|                              |                                   |       | MCL      | 2  | 0/2 (0%) | 1/2 (50%)      |                  |
| Berger et al., 2008 [21]     | Pidilzumab                        | I     | CLL      | 3  | 0/3 (0%) | 0/3 (0%)       | N/A              |
|                              |                                   |       | DLBCL    | 2  | 0/3 (0%) | 0/2 (0%)       |                  |
|                              |                                   |       | FL       | 1  | 1/1 (100%) | 1/1 (100%)   |                  |
| Ansell et al., 2009 [23]     | Ipilimumab                        | I     | FL       | 14 | 0/14 (0%) | 1/14 (7%)      | NCT00089076     |
|                              |                                   |       | DBLCL    | 3  | 1/3 (33%) | 1/3 (33%)      |                  |
|                              |                                   |       | MCL      | 1  | 0/1 (0%)   | 0/1 (0%)       |                  |
| Bashey et al., 2009 [22]     | Ipilimumab                        | I     | MCL      | 1  | 0        | 1/1 (100%)     | NCT0060372      |
|                              |                                   |       | CLL      | 2  | 0        | 0/2 (0%)       |                  |
| Westin et al., 2014 [31]     | Pidilizumab and rituximab         | II    | FL       | 29 | 15/29 (52%) | 19/29 (66%)   | NCT00904722     |
| Ansell et al., 2016 [29]     | Nivolumab and ipilimumab          | Ib    | B-NHL    | 15 | 0/15 (0%) | 3/15 (20%)     | NCT01592370     |
| Lesokhin et al., 2016 [26]   | Nivolumab                         | Ib    | FL       | 10 | 1/10 (10%) | 4/10 (40%)     | NCT01592370     |
|                              |                                   |       | MCL      | 4  | 0/4 (0%)   | 0/4 (0%)       |                  |
|                              |                                   |       | MZL      | 1  | 0/1 (0%)   | 0/1 (0%)       |                  |
|                              |                                   |       | DLBCL    | 11 | 2/11 (18%) | 4/11 (36%)     |                  |
| Ding et al., 2017 [25]       | Pembrolizumab                     | II    | CLL      | 16 | 0/16 (0%) | 0/16 (0%)      | NCT02332980     |
|                              |                                   |       | CLL with RT | 9  | 1/9 (11%) | 4/9 (44%)      |                  |
| Ding et al., 2017 [24]       | Pembrolizumab                     | II    | FL       | 18 | 0/18 (0%) | 2/18 (11%)     | NCT02332980     |
|                              |                                   |       | MZL      | 2  | 0/2 (0%)   | 0/2 (0%)       |                  |
| Nastoupil et al., 2017 [30]  | Pembrolizumab and rituximab       | II    | FL       | 25 | 12/25 (48%) | 16/25 (64%)    | NCT02446457     |
| Younes et al., 2017 [36]     | Atezolizumab, Obinutuzumab and Bendamustin | Ib/II | FL       | 15 | 10/15 (67%) | 12/15 (80%)    | NCT02596971     |
| Ansell et al., 2019 [27]     | Nivolumab                         | II    | auto-HCT failed DLBCL | 87 | 3/87 (3%) | 9/87 (10%)     | NCT02038933     |
|                              |                                   |       | auto-HCT ineligible DLBCL | 34 | 0/34 (0%) | 1/34 (3%)      |                  |
### Table 1. Cont.

| Study                      | Treatment                              | Phase | Disease          | N    | CR       | ORR     | Trial ID (NCT) |
|----------------------------|----------------------------------------|-------|------------------|------|----------|---------|----------------|
| Khouri et al., 2018 [40]   | Ipilimumab and lenalidomide            | II    | FL (allo-HSCT)   | 2    | 1/2 (50%)| 2/2 (100%)| NCT01919619   |
|                            |                                        |       | MCL (allo-HSCT)  | 3    | 2/3 (67%)| 3/3 (100%)|                |
|                            |                                        |       | DLBCL (allo-HSCT) | 1   | 0/1 (0%) | 1/1 (100%)|                |
|                            |                                        |       | CLL (allo-HSCT)  | 2    | 0/2 (0%) | 0/2 (0%)  |                |
|                            |                                        |       | MCL (auto-HSCT)  | 2    | 2/2 (100%)| 2/2 (100%)|                |
|                            |                                        |       | FL (auto-HSCT)   | 1    | 1/1 (100%)| 1/1 (100%)|                |
| Palomba et al., 2017 [35]  | Atezolizumab and obinutuzumab          | lb    | FL               | 26   | N/A      | 57%     | NCT02220842   |
|                            |                                        |       | DLBCL            | 23   | N/A      | 16%     |                |
| Younes et al., 2018 [37]   | Atezolizumab, Rituximab and CHOP       | I/II  | DLBCL            | 40   | 31/40 (78%)| 35/40 (88%)| NCT02596971   |
| Armand et al., 2019 [28]   | Pembrolizumab                          | Ib    | PMBCL            | 21   | 7/21 (33%)| 48%     | NCT01953692   |
|                            | Pembrolizumab                          | II    | PMBCL            | 53   | 7/53 (13%)| 45%     | NCT02576990   |
| Bond et al., 2019 [38]     | Nivolumab and lenalidomide             | I     | B-cell lymphoma *| 10   | 1/10 (10%)| 3/10 (30%)| NCT03015896   |
| Casulo et al., 2019 [39]   | Durvalumab monotherapy or              | I/II  | DLBCL            | 38   | 3/38 (8%) | 7/38 (18%)| NCT02733042   |
|                            | in combination with lenalidomide       |       | FL               | 22   | 6/22 (27%)| 13/22 (59%)|                |
|                            | ± rituximab or                         |       |                  |      |          |         |                |
|                            | ± rituximab ± bendamustine             |       |                  |      |          |         |                |
| Younes et al., 2019 [41]   | Nivolumab and ibrutinib                | I/Ia  | CLL/SLL          | 36 (30 CLL) | 0/36 (0%)| 22/36 (61%)| NCT02329847   |
|                            |                                        |       | RT               | 20   | 2/20 (10%)| 13/20 (65%)|                |
|                            |                                        |       | FL               | 40   | 4/40 (10%)| 13/40 (33%)|                |
|                            |                                        |       | DLBCL            | 45   | 7/45 (16%)| 16/45 (36%)|                |
| Zinzani et al., 2019       | Nivolumab and brentuximab vedotin      | I/II  | PMBCL            | 30   | 11/30 (37%)| 22/30 (73%)| NCT02581631   |
| Frigault et al., 2020 [47] | Pembrolizumab after auto-SCT           | II    | DLBCL            | 29   | 17/29 (59%)| 17/29 (59%)| NCT02362997   |
| Herrera et al., 2020 [45]  | Durvalumab and ibrutinib               | Ib/II | FL               | 27   | 1/27 (4%) | 7/27 (26%)| NCT02401048   |
|                            |                                        |       | GCB DLBCL        | 16   | 1/16 (6%) | 2/16 (13%)|                |
|                            |                                        |       | Non-GCB DLBCL    | 16   | 5/16 (31%)| 6/16 (38%)|                |

*N* = number of patients, CR = complete response, ORR = overall response rate, N/A = not available, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, MZL = marginal zone lymphoma, FL = follicular lymphoma, MCL = mantle cell lymphoma, SLL = small lymphocytic leukemia, PMBCL = primary mediastinal large B-cell lymphoma, RT = Richter’s transformation, CHOP = cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone, auto-HSCT = autologous hematopoietic stem cell transplantation, allo-HSCT = allogeneic hematopoietic stem cell transplantation, GCB = Germinal center B-cell, *5 patients were diagnosed with DLBCL.*
Together, these results indicate that, unlike in HL, results for ICB in B-NHL are thus far disappointing, except for PMBCL. Although combinations, such as with rituximab or lenalidomide, seem to increase response rates, it remains to be elucidated whether a true synergistic, or at least additive, effect exists.

2.2. Bispecific Antibody Therapy

Multiple studies have investigated BsAbs in B-NHL (Table 2). The first phase I study of blinatumomab in relapsed/refractory B-NHL showed an overall response rate (ORR) of 80% for FL (15 patients), 71% for MCL (seven patients) and 55% for DLBCL (11 patients), with a median DOR of 404 days [48]. Similar results were reported in a phase II study for relapsed/refractory DLBCL using blinatumomab [49]. Of the 21 patients that received the target dose, 9 obtained a response (ORR 43%), of which four had CR, with a median DOR of 11.6 months and progression free survival (PFS) of 3.7 months (median follow-up of 15.0 months) [49]. In line with this, Coyle et al. showed an ORR of 37% and CR of 22% in relapsed/refractory B-NHL, of which the majority of patients were diagnosed with DLBCL (n = 34 of 41 included patients) [50]. Although these first results with blinatumomab were encouraging, albeit most responses were partial, preliminary data show that response rates can be increased by using a combination of blinatumomab and lenalidomide [51]. This combination resulted in an ORR of 83% with 50% CR in 18 relapsed/refractory B-NHL patients including DLBCL (seven patients), MCL (three patients), FL (three patients) and MZL (one patient) [51]. Blinatumomab has also been tested as a consolidation treatment in DLBCL. Patients received first-line treatment consisting of six cycles of rituximab and chemotherapy followed by at least one or two cycles of blinatumomab. Of 28 evaluable patients, 25 had a response (ORR 89%) after blinatumomab treatment, and with a median follow-up time of 8.6 months, 93% of patients were still alive [52].

Treatment with mosunetuzumab, a CD3xCD20 BsAb, resulted in an ORR of 64% and CR of 42% in 64 patients with indolent B-NHL, mainly consisting of FL patients [53]. In contrast, the ORR and CR rate were significantly lower (34% and 18%, respectively) in 119 patients with more aggressive B-NHL (DLBCL or transformed FL) [53]. Surprisingly, patients who had relapsed or were refractory to CAR T-cell therapy could mount effective anti-lymphoma responses upon treatment with mosunetuzumab, with an ORR of 44% [53]. Preliminary results with epcoritamab, a CD3xCD20 bispecific that is administered subcutaneously, showed promising findings in patients with DLBCL and FL. Although cohorts are still small, five out of nine patients with high grade B-cell lymphoma that received dosages ≥6 mg had a response (ORR 56%), of whom four had CR [54]. In a small cohort of six FL patients that received ≥0.76 mg, all obtained a PR (ORR 100%) [54]. Another trial using CD3xCD20 bispecific antibody REGN1979 showed that B-NHL patients who had previously received an anti-CD20 antibody had an ORR of 26% with 80 days as median DOR [55]. In this cohort, objective responses were reported in patients with DLBCL (22 patients), FL (11 patients), MCL (two patients) and MZL (two patients) [55]. A recent update of this study showed promising data for FL and DLBCL. Administration of ≥5 mg of REGN1979 led to responses in 26 of 28 FL patients (ORR 93%), with CR in 21 patients (75%) [56]. In DLBCL patients that had not received CAR T-cell therapy, responses were mainly observed in increased REGN1979 dosages of ≥ 80 mg; six out of 10 patients showed a response, which were all CRs. However, after the failure of CAR T-cell therapy, responses were only observed in seven out of 21 patients (ORR 33%), of which five were CR [56]. Additionally, combinations of a CD3xCD20 antibody and an anti-CD20 antibody seem feasible. In a phase I trial, the CD3xCD20 BsAb glofitamab was given concurrently with obinutuzumab. Patients that were included had aggressive B-NHL or FL. In the 21 included patients, the ORR and CR was 48% and 43%, respectively; the 10 patients that received the highest dosage of glofitamab showed remarkable high responses: an ORR of 90% with a CR rate of 80% [57].

In general, these studies show that reasonable responses against B-NHL can be elicited by BsAb monotherapy. Although patients with indolent lymphomas such as MCL and MZL are currently underrepresented, enhanced efficacy of BsAbs towards indolent lymphomas compared to
DLBCL is observed (Table 2). For CLL, no clinical data are available, although in vitro studies seem promising [58–62]. In FL and DLBCL, combinations of BsAbs with chemotherapy, lenalidomide and/or CD20 antibodies are favorable, although final results of these trials have to be awaited [51,52].

### Table 2. Reported studies of bispecific antibodies in B-NHL.

| Study                          | Treatment                          | Phase | Disease          | N  | CR  | ORR  | Trial ID (NCT) |
|-------------------------------|------------------------------------|-------|------------------|----|-----|------|----------------|
| Goebeler et al., 2016 [46]     | Blinatumomab                        | 1     | FL               | 15 | *   | 6/15 (40%) | NCT02274742    |
|                               |                                    |       | MCL              |    | 7   | 3/7 (43%) |                |
|                               |                                    |       | DLBCL            | 11 | *   | 4/11 (36%) |                |
| Viardot et al., 2015 [45]     | Blinatumomab                        | 2     | DLBCL            | 21 |     | 4/21 (19%) | NCT01741792    |
| Bannerman et al., 2017 [55]   | REGN1979 (CD3xCD20)                 | 1     | DLBCL            | 22 |     | 0/22 (0%)  | NCT02280951    |
|                               |                                    |       | FL               | 11 |     | 0/11 (0%)  |                |
|                               |                                    |       | MZL              | 2  |     | 0/2 (0%)   |                |
|                               |                                    |       | MCL              | 2  |     | 0/3 (0%)   |                |
| Katz et al., 2019 [55]        | Blinatumomab after R-CHOP           | 2     | DLBCL            | 28 |     | NA       | NCT03023878    |
| Moschhausser et al., 2019 [57]| Glofitamab and obinutuzumab *       |       | B-NHL ** (all included) | 21 |     | 9/21 (43%) | NCT03075996    |
|                               |                                    |       | B-NHL ** (highest glofitamab dose) | 10 |     | 8/10 (80%) |                |
| Poh et al., 2019 [51]         | Blinatumomab and lenalidomide       | 1     | B-NHL            | 18 |     | 50%      | NCT02568553    |
| Schaner et al., 2019 [53]     | Mozosunetumab 1/1b                  |       | indolent B-NHL *** | 64 |     | 27/64 (42%) | NCT02500407    |
|                               |                                    |       | aggressive B-NHL *** | 119|     | 22/119 (18%) |                |
|                               |                                    |       | FL (≥5 mg)       | 28 |     | 21/28 (75%) |                |
|                               |                                    |       | FL (≥80 mg)      | 16 |     | 11/16 (69%) |                |
|                               |                                    |       | DLBCL (no prior CAR, ≥5 mg) | 30 |     | 9/30 (30%)  |                |
|                               |                                    |       | DLBCL (no prior CAR, ≥80 mg) | 10 |     | 6/10 (60%)  |                |
|                               |                                    |       | DLBCL (relapse after CAR, ≥5 mg) | 23 |     | 5/23 (22%)  |                |
|                               |                                    |       | DLBCL (relapse after CAR, ≥80 mg) | 21 |     | 5/21 (24%)  |                |
| Bannerman et al., 2020 [56]   | REGN1979                            | 1     | FL               | 21 (33%) | 7  | 21 (55%) | NCT02280951    |
|                               |                                    |       | MCL              | 10 (80%) | 6  | 10 (60%) |                |
|                               |                                    |       | DLBCL            | 11 (55%) | 9  | 11 (55%) |                |
| Coventry et al., 2020 [50]    | Blinatumomab                        | 2     | B-NHL ***       | 41 (22%) | 9 | 41 (22%) | NCT02910063    |
| Hutchings et al., 2020 [54]   | Subcutaneous epcoritamab (GEN3013, CD3xCD20) | 1/2 | DLBCL/HGBCL      | 9  |     | 4/9 (44%)  | NCT03625037    |
|                               |                                    |       | FL               | 6  |     | 3/6 (50%)  |                |

N = number of patients, CR = complete response, ORR = overall response rate, N/A = not available, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, MZL = marginal zone lymphoma, FL = follicular lymphoma, MCL = mantle cell lymphoma, B-NHL = B-cell non-Hodgkin lymphoma, HGBCL = high-grade B-cell lymphoma, NA = not available. * n reflects only the number of patients that reached the target dose at 60 µg/m²/day, ** include DLBCL, primary mediastinal large B-cell lymphoma, MCL, RT, and (transformed) FL, *** indolent NHL mainly included FL. Aggressive B-NHL mainly includes DLBCL and transformed FL, **** 34 of 41 DLBCL, other 7 patients were classified as other lymphomas.

2.3. Chimeric Antigen Receptor Therapy

Virtually all CAR construct studies in trials thus far are directed against the pan B-cell marker CD19 and contain either the intracellular domain of the co-stimulatory receptor CD28 (28z) or 4-1BB (BBz). Since 28z and BBz CARs are functionally different, we will discuss them separately (Table 3). Currently all CAR trials use a one-time infusion strategy. As only CRs are associated with long-term responses, we will focus on CR rates [63–65]. The first 28z CAR T-cell trials in B-NHL demonstrated varying CR rates of 0–25% [66–69]. The minority of patients that did reach CR achieved long-lasting remissions, with DORs ranging from 8 weeks to 15 months [66–69]. Since then, CAR T-cell therapy for B-NHL has been further optimized as demonstrated by improved CRs ranging from 22% to 62% in subsequent trials [70–73]. The DOR in these studies ranged from 6 weeks to 52.8 months [70–73]. Large scale clinical trials recruiting patients with specific types of B-NHL allowed better determination of the efficacy per tumor type. In DLBCL patients (n = 108) treated with 28z CAR, a CR rate of 58% was observed. The DOR was 11 months (PFS of 5–9 months) [74]. Similarly, an interim analysis from the ZUMA-5 trial demonstrated a CR rate of 79% in 80 FL and 14 MZL patients, and ongoing responses were observed in 68% of the patients [75]. In another study, 60 evaluable MCL patients demonstrated at least a CR rate of 67% after 7 months of follow-up. The median time to initial response was 1 month, and at median follow-up of 12.3 months, 57% of the 60 evaluable patients were still in remission [65].
Early and small trials (that recruited ≤ 50 patients) using BBz CAR T-cells yielded CRs of 19.5–87.5% [76–80]. Lasting DORs were obtained and ranged between 7.7–39.9 months [76–80]. A large-scale study demonstrated efficacy of BBz CAR T-cells in 93 DLBCL patients, of which 40% had CR. Twelve months after the initial response, the relapse free survival was 65% amongst all patients, and 79% among patients with CR [64]. Another large study recruited 342 DLBCL patients, of which 255 patients were evaluable for response. The CR was 53% with a median DOR of 13.3 months. Patients had a PFS of 6.8 months with a median OS of 19.9 months [81].

To our knowledge, only one study has directly compared the clinical efficacy of 28z and BBz CARs. Three patients received 28z CARs and six patients received BBz CARs. Unfortunately, the 28z CAR was not well tolerated. Eight patients were evaluable for response, of which one had MZL (received ibrutinib as a prior therapy received BBz CARs, which resulted in CR in 45.5% [83]. Improved responses may be the result of enhanced T-cell engraftment and CAR T-cell generation, both of which correlated with clinical response [84]. Cao et al. treated 11 patients with BBz CARs and nivolumab, of which 10 patients had DLBCL and one had Burkitt lymphoma. The CR was 45.5% with a median PFS of 6 months [85].

**Table 3.** Chimeric antigen receptor therapy clinical studies.

| Study | CAR type | Phase | Disease | N | CR | ORR | Trial ID (NCT) |
|-------|----------|-------|---------|---|----|-----|---------------|
| Till et al., 2008 [66] | anti-CD20 | I | FL | 7 | 2/7 (29%) | 3/7 (43%) | NCT00012207 |
| Brentjens et al., 2011 [69] | anti-CD19 | I/II | CLL | 7 | 0/7 (0%) | 0/7 (0%) | NCT00466531 |
| Kochenderfer et al., 2012 [67] | anti-CD19 | I/II | FL, CLL | 4 | 3/4 (75%) | 3/4 (75%) | NCT00924326 |
| Kochenderfer et al., 2013 [68] | anti-CD19 | I | DLBCL, MCL | 4 | 0/4 (0%) | 0/4 (0%) | NCT01087294 |
| Kochenderfer et al., 2015 [70] | anti-CD19 | I/II | CLL, MZL, DLBCL | 4 | 0/4 (0%) | 0/4 (0%) | NCT00924326 |
| Ramos et al., 2016 [72] | anti-k light chain | I | CLL, MCL | 2 | 0/2 (0%) | 0/2 (0%) | NCT00881920 |
| Wang et al., 2016 [76] | anti-CD19 (1st gen) | I/II | FL, MCL, MZL | 5 | 0/0 (0%) | 0/0 (0%) | NCT01318317 |
| | anti-CD19 (2nd gen) | I | DLBCL, MCL, MZL | 4 | 3/4 (75%) | 3/4 (75%) | NCT01613749 |
| Kochenderfer et al., 2017 [71] | anti-CD19 | I/II | FL, MCL | 2 | 2/2 (100%) | 2/2 (100%) | NCT00924326 |
| Geyer et al., 2018 [73] | anti-CD19 | I | CLL | 8 | 2/8 (25%) | 2/8 (25%) | NCT01416974 |
| Locke et al., 2018 [74] | anti-CD19 | I/II | DLBCL | 101 | 59/101 (58%) | 84/101 (83%) | NCT02348216 |
| Jacobsen et al., 2020 [75] | anti-CD19 | II | FL, MZL | 80 | 64/80 (80%) | 76/80 (95%) | NCT03105336 |
| Wang et al., 2020 [76] | anti-CD19 | II | MCL | 60 | 40/60 (67%) | 56/60 (93%) | NCT02631313 |
| Kalos et al., 2011 [67] | anti-CD19 | I | CLL | 3 | 2/3 (67%) | 3/3 (100%) | NCT00295477 |
| Porter et al., 2013 [78] | anti-CD19 | I | CLL | 14 | 4/14 (29%) | 4/14 (29%) | NCT01029386 |
| Fraietta et al., 2016 [79] | anti-CD19 | I/II | CLL | 3 | 1/3 (33%) | 1/3 (33%) | NCT01747486 |
| Schuster et al., 2017 [79] | anti-CD19 | I | FL, DLBCL | 14 | 6/14 (42%) | 10/14 (71%) | NCT02000834 |
| Fraietta et al., 2018 [79] | anti-CD19 | I | CLL | 41 | 8/41 (20%) | 16/41 (39%) | NCT01274786 |
| Abramson et al., 2019 [81] | anti-CD19 | I | DLBCL | 255 | 135/255 (53%) | 186/255 (73%) | NCT02631044 |
Based on the clinical results described above, it becomes clear that CAR T-cell therapy can yield impressive and lasting responses in B-NHL patients. Especially in DLBCL, FL, MCL, and MZL, CAR T-cell therapy yields high CR rates but still falls well below of what is observed in ALL, with the exception of very few clinical trials (Table 3). The most striking observation is that the lowest CRs are observed in patients with CLL in both 28z and BBz CAR T cell studies. Perhaps the low efficacy of CAR T cell therapy in CLL can be explained by the coinciding immune dysfunction that is observed in CLL patients. In the next section, we will discuss this in-depth for each type of B-NHL discussed before.

3. T-Cell Immune Surveillance in NHL

From the clinical observations, it follows that efficacy of autologous T-cell-based cellular therapies differs between lymphoma subtypes and between treatment modalities, with the lowest responses for ICB, and that in general, such treatments are less effective in the discussed lymphoma entities than in HL (ICB) and ALL (BsABs and CAR T-cells). In recent years, it has become apparent that patients with B-NHL acquire alterations in T-cell differentiation and function. These T-cell abnormalities affect responses to cellular therapies but are not similar among the different lymphoma subtypes. In this section, we predominantly focus on changes in phenotype and function of T-cells in B-NHL.

3.1. Mutational Load in B-NHL

Successful ICB depends on recognition of tumor cells by immune effector cells such as T-cells. These T-cells often recognize antigens that arise due to mutations within tumor cells. Indeed, a clear correlation exists between tumor mutational load and efficacy of ICB [89,90]. Although tumor-specific T-cells have been found in a subset of CLL and MCL patients [91–93], the mutational load of B-cell lymphomas is remarkably lower than tumors known to be sensitive to ICB treatment [89]. These results imply that only a subset of lymphomas with high tumor mutational burden might be sensitive to ICB.

3.2. T-Cell Skewing

T-cells can be subdivided into naive (CD45RA+CD27+/CCR7+), memory (including central memory (CD45RA−CD27+/CCR7+), effector memory (CD45RA−CD27−/CCR7−)) T-cells, and terminally differentiated effector T-cells (CD45RA+/CD27−/CCR7−) [94,95]. Of these subsets, it is the memory T-cell subset that persists in vivo and has high proliferative capacity, while effector cells have superior effector function [96]. Skewing of these T-cell subsets has mainly been studied in CLL, FL and MZL, although research has focused on different compartments within these lymphoma types, whereas observations of T-cell skewing in CLL are mostly derived from analyzing peripheral blood (PB), for other lymphomas, lymph node-(LN)-derived T-cells have been the main focus.

### Table 3. Cont.

| Study                  | CAR type      | Phase | Disease | N   | CR | ORR | Total ID (NCT)               |
|------------------------|---------------|-------|---------|-----|----|-----|----------------------------|
| Cao et al., 2019 [85]  | anti-CD19 **  | N/A   | DLBCL   | 10  | 5/10 (50%) | 9/10 (90%)   | ChiCTR-ONN-16009962, ChiCTR1800019288 |
| Hirayama et al., 2019  | anti-CD19 I/II| FL    | FL ***  | 8   | 7/8 (88%)  | 7/8 (88%)    | NCT01865617   |
| Schuster et al., 2019  | anti-CD19 II  | DLBCL | 93     | 40/93 (43%) | 52/93 (56%) | NCT02445248 |
| Siddiqi et al., 2019   | anti-CD19 I/II| CLL   | 22     | 10/22 (64%) | 18/22 (82%) | NCT03331198 |
| Ying et al., 2019 [82] | anti-CD19 (4-1BB or CD28) | II    | MZL    | 1  | 1/1 (100%) | 1/1 (100%)   | NCT03528421   |
| Gauthier et al., 2020  | anti CD19 I/II| CLL   | 19     | N/A | 14/17 (88%) | 10/19 (56%)  | NCT01865617   |

CAR = chimeric antigen receptor, N = number of patients, CR = complete response, ORR = overall response rate, N/A = not available, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, MZL = marginal zone lymphoma, FL = follicular lymphoma, MCL = mantle cell lymphoma, n/a = not available. * Patients were selected based on minimal residual disease (MRD) after purine-based chemotherapy. ** Patients received nivolumab during treatment. *** Transformed FL. **** Ibrutinib treated.
In PB of CLL, absolute CD4+ and CD8+ numbers are increased [97–100], and CD4:CD8 ratios are inverted upon disease progression [101,102]. In addition, CD4+ and CD8+ effector memory T-cells are expanded at the cost of naive T-cells [98,101–103]. Compared to PB, in LN of CLL patients, an increased amount of central memory T-cells were observed [104]. Both T helper (Th)1 and Th2 cells are increased in absolute numbers [103] but data on skewing of Th1/Th2 balance are conflicting. Skewing towards a more pro-tumoral Th2 phenotype in which CD4+ T-cells produce interleukin (IL) 4 is described [105–107], while skewing in both progressive and non-progressive CLL patients towards a Th1 phenotype also has been reported, in which CD4+ T-cells produce more interferon y (IFNy), possibly contributing to an anti-tumor response [103,108].

Th2 and Th17 cells are increased in LN of FL patients [109,110]. Although absolute numbers of Th1 cells were small, high Th1 numbers correlated with rapid transformation [111]. Furthermore, CD4+ tumor-infiltrating T helper cells from FL patients showed a skewing towards an effector memory phenotype, while naive and central memory cells were decreased [110]. Decreases in circulating CD4+ T-cells were found in PB of FL patients, attributable to a decrease in naive T-cells [105]. Although CD8+ numbers were normal, a skewing towards T effector memory cells re-expressing CD45RA (Temra) cells could be observed within the CD8+ compartment [105].

T-cell skewing is observed in MZL as well. T-cell infiltrates in mucosa-associated lymphoid tissue (MALT) lymphoma predominantly have a Th1 phenotype, while in some cases CD8+ T-cells were observed as the main infiltrating T-cell type [112–115]. Interestingly, lower absolute numbers of circulating CD4+ T-cells were found in extranodal MZL with predominance of the naïve phenotype [105]. Similar to CLL, circulating CD8+ T-cells in MZL had a terminally differentiated phenotype [105].

It thus seems that T-cells from B-NHL patients are skewed towards a more antigen-experienced phenotype, and have a disturbed Th1/Th2 balance, although the latter varies between different B-NHL subtypes.

Skewing of T-cells can greatly influence T-cell therapy. Since memory T-cells are the driving force of T-cell persistence in vivo, and their presence is correlated with highly durable clinical remissions in CAR T-cell therapy, it is plausible that the composition of the patients’ T-cell subsets may influence the therapy outcome. For CAR T-cells, indeed, persistence and peak expansion of CAR T-cells in vivo are predictors of favorable clinical outcome in B-NHL, coinciding with the presence of memory-like T-cells [67,76,78,116]. This is further emphasized by the effect of the generation of CAR T-cells from different T-cell subsets, with CAR T-cells generated from central memory T-cells showing most favorable responses [117]. Additionally, predicting the clinical outcome of CAR T-cell therapy in CLL patients is possible by analyzing the apheresis product before generating CAR T-cells. Elevated numbers of memory-like T-cells, characterized by CD8+/CD27+/CD45RO−, were found in the product in CLL patients that do respond to therapy [76]. Furthermore, CAR T-cell products from CLL patients that had elevated levels of memory-like CD8+ CAR T-cells negative for PD-1 correlated with improved clinical outcome [76]. For BsAb therapy, it has been implicated that effector memory T-cells are responsible for the activity [81]; however, this such a correlation could not be confirmed in BsAb trials in B-NHL.

3.3. Inhibitory Receptor Expression and Exhaustion in B-NHL

Chronic stimulation and inflammatory signals can induce exhaustion of T-cells leading to loss of effector function. Multiple exhaustion markers have been extensively studied, including PD-1, T-cell immunoglobulin, and mucin domain-containing protein 3 (TIM3), T-cell immunoglobulin and ITIM domain (TIGIT), CTLA-4, and lymphocyte activation gene-3 (LAG3), and negatively regulate T-cells via different mechanisms as extensively reviewed in [118]. Ligands for exhaustion markers on T-cells are often expressed on tumor cells or bystander cells in the TME and have been studied for DLBCL, CLL, FL, MCL and MZL.

In DLBCL, an estimated 11–24% of all patients show high expression of PD-L1 on tumor cells and high PD-1 expression on T-cells, which are associated with poor patient survival [116,119–124]. Additionally, PD-L1 expression on DLBCL cells correlates with PD-1 expression on T-cells [121].
Blocking PD-L1 promoted the proliferation and production of IFNγ in T-cells demonstrated by an allogenic co-culture set-up [116]. Sufficient T-cell infiltration in DLBCL tumors may be required for successful anti-PD-L1/PD-1 therapy [125]. However, expression of PD-L1 and PD-1 may not always be responsible for the inhibitory effect in T-cells in DLBCL [125]. In addition, in some DLBCL cases, higher frequencies of CD4+TIM3+ and CD8+TIM3+ T-cells were observed [124,126], correlating with disease severity [124]. Additionally, T-cells in DLBCL may display increased expression of CD244 [127]. Furthermore, reduced expression of IFNγ, tumor necrosis factor α (TNFα), and IL-2 was observed intratumoral T cells in DLBCL, which co-expressed inhibitory receptor TIGIT and PD-1 [127]. Immunomodulatory receptor LAG3 and CTLA-4 may play lesser roles in DLBCL, as no differences in LAG3 expression on immune cells in the tumor microenvironment were observed compared to healthy donors [128]. Interestingly, CTLA-4 expression on T-cells in DLBCL may actually have a favorable prognosis [129].

Additionally, in CLL, exhaustion may play a role. T-cells derived from these patients display increased expression of PD-1, BTLA, CTLA-4, TIGIT, CD160 and CD244 [99,103,130–133]. However, production of cytokines by T-cells is similar to that of healthy controls, implying that T-cells in CLL do not reflect the classic exhausted phenotype despite expression of exhaustion marker [132]. In FL, TILs are shown to have increased expression of PD-1, TIM-3, TIGIT and LAG-3 [127,131,134–139]. In contrast to CLL, these T-cells often show reduced production of IFNγ, IL-2, TNFα, granzyme B and perforin upon T-cell stimulation, indicating that these cells indeed might be exhausted [127,136–138,140]. Unlike other B-NHL subtypes, expression of PD-L1 on tumor cells was mostly absent in CLL and FL [141].

In MCL, intratumoral T-cells display significantly higher expression of TIGIT, CD244, and LAG3 compared to controls, especially in the effector-memory compartment [127]. Only a subset of MCL patients expressed the TIGIT ligand CD155 while no PD-L1 on tumor cells was detected. However, PD-L1 was expressed by intratumoral macrophages [127]. In contrast, others have shown that PD-L1 could be detected on MCL cells at both messenger RNA and protein level as well, although its receptor PD-1 was not significantly highly expressed on T-cells compared to healthy donors (HD) [142,143]. Conversely, another study has reported PD-L1 to be rarely expressed on MCL cells [144]. Thus, the role of PD-1/PD-L1-axis in MCL remains a subject of debate since many studies have reported opposing results.

In MZL, PD-1 and PD-L1 also might play a role. PD-L1 was expressed by splenic MZL cells [115], and its ligand PD-1 was found expressed on T-cells in extranodal MZL and MALT lymphoma [145,146].

Despite high expression of exhaustion markers on B-NHL-derived T-cells, the efficacy of ICB is disappointing, which may not only be explained by a relative low tumor mutational load (see Section 3.1) but also by low expression of inhibitory ligands such as PD-L1 on the tumor cells. In contrast, tumor cells in HL and PMBCL acquire a copy gain or amplification of 9p24.1 leading to aberrant expression of PD-L1 [147–149]. In PMBCL, high PD-L1 expression also correlated with PFS after pembrolizumab treatment. Thus, low expression of PD-L1 in B-NHL may in part explain the failure of ICB in these other B-NHL subtypes. However, ICB does not seem to resolve or prevent T-cell exhaustion on its own. ICB may only be successful in a subset of patients where expression of inhibitory ligands is high, as in PMBCL patients and a subset of DLBCL patients.

T-cell exhaustion can influence the efficacy of CAR T-cell therapy as well. For example, five patients with the highest PD-1/PD-L1 interactions showed no response to therapy, or quickly relapsed in a CAR T-cell trial for DLBCL patients [64]. In addition, 11 patients with the highest LAG3 levels also did not respond or relapsed [64]. Similar results were observed in another CAR T-cell trial in DLBCL patients [79]. CLL patients responding to CAR T-cell therapy had increased populations of PD-1 negative memory T-cells [76]. These results indicate, perhaps unsurprisingly, that T-cell exhaustion is a major cause of failure to CAR T-cell therapy.

It is currently unclear what role exhaustion plays in the treatment of patients with BsAbs since this has not been investigated extensively to our knowledge.
3.4. Functional Defects

Chronic stimulation of T-cells by tumors can lead to functional impairments such as defective cytokine production, activation, synapse formation and cytotoxic potential. For example, impaired formation of the immunological synapse impairs CAR T-cell efficacy, and therapy effectiveness can even be predicted by assessing the quality of synapse formation between the CAR T-cell and target cells [150]. The functionality of T-cells has mainly been investigated in CLL, FL and MZL.

In CLL, T-cells retain cytokine production, but have impaired synapse formation, proliferation, activation, and cytotoxicity [136,151,152].

In FL, similar defects have been reported. Upon T-cell receptor (TCR) triggering, TILs in FL have a defective proliferative capacity [134,140], impaired motility as well as synapse formation [153,154]; the latter was also reported in transformed FL and de novo DLBCL [153]. Despite these dysfunctions, 3D confocal imaging revealed increased numbers of granzyme B positive CD8+ T-cells in FL samples compared to reactive lymph nodes [155]. These T-cells were shown to form synapses at the follicle border, implying that they can still be cytotoxic [155].

In MZL, induction of MALT lymphoma by Helicobacter pylori may impair T-cell functionality demonstrated by reduced killing of autologous Epstein–Barr virus B-cells [156].

It can thus be concluded that different B-NHL subtypes harbor different functional defects, although most seem to have acquired defective cytotoxic and proliferative capacities as well as impaired synapse formation. Nevertheless, it remains to be elucidated whether this is also the case for other B-NHL subtypes.

3.5. T-Cell Metabolism in B-NHL

It has been widely accepted that T-cell metabolism dictates function and development as extensively reviewed previously [151,152]. In short, naive T-cells utilize many different metabolites for their energy needs, while effector T-cells rely on glycolysis as the primary metabolic pathway, and memory T-cells rely on the oxidative phosphorylation of lipids [152]. It is important to note that access to these metabolites may be restricted as a result of competition by proliferating tumor cells in the tumor microenvironment [157]. Especially in the more aggressive forms of B-NHL, nutrient restriction may induce T-cell dysfunction. While lymphoma cells have high activity of oxidative phosphorylation or glycolysis (or both), care must be taken not to overestimate metabolic activity of B-NHL cells based on data derived from cell lines that may have adapted themselves to the nutrient-rich medium of in vitro cultures [158,159]. Currently, data on T-cell metabolism in DLBCL, FL, MCL, or MZL are lacking and most results regarding T-cell metabolism in B-NHL are derived from analysis of CLL patient material. In these data, it has been shown that T-cells have impaired expression of the glucose transporter Glut1, which coincides with reduced glucose uptake and mitochondrial defects, which impact CAR T cell therapy [160,161]. Thus, since lymphoma cells can exert metabolic pressure and metabolism is important for the effector function of T-cells, it is highly likely that reduced glycolysis and impaired mitochondrial fitness in T-cells contribute to the decreased efficacy of T-cell-based therapies in CLL, and possibly in DLBCL, FL, MCL, or MZL as well [151].

3.6. Regulatory T-Cells and T Follicular Helper Cells

Regulatory T-cells (Tregs), a subset of CD4+ T-cells that express forkhead box protein P3 (FOXP3), play a major role in preventing autoimmunity by dampening immune responses. However, Tregs have conversely been implicated in hindering effective anti-tumor immunity as well [162]. Tregs have been implicated to play a role in DLBCL, CLL, FL and MZL, possibly being responsible for suboptimal responses observed in T-cell mediated therapy.

Although Tregs are classified as immunosuppressive, increased numbers of Tregs correlate with favorable prognosis in DLBCL and FL, where low Treg numbers can predict transformation of FL to DLBCL [163–170]. For FL, it has been shown that these Tregs are suppressive as they
inhibited proliferation and cytokine production of T-cells [166]. Tregs directly suppress proliferation of B-cells [171], and perhaps leukemic cells as well. Therefore, it is possible that Tregs inhibit the malignant FL or DLBCL clone, resulting in better prognosis. In CLL, many studies have shown that Treg compartments are expanded compared to controls, and correlate with advanced disease and number of circulating CLL cells [98,103,105,172–174]. Furthermore, it has been shown that in CLL, increased Treg numbers correlate with shorter time to first treatment, indicating a negative effect of these cells on tumor control [175]. In MZL, increased amounts of Tregs could be found in MALT lymphomas [176]. However, this could not be recapitulated for other forms of MZL [177]. The above mentioned observations indicate that Tregs play an important role in B-NHL, but their exact place in disease progression or regression is not well defined.

T follicular helper cells (Tfh), characterized as CD4\(^+\)CXCR5\(^+\)PD-1\(^+\), can play a role in support of the TME and are well studied in DLBCL and FL. For DLBCL, Tfh cells seem to promote DLBCL cell growth and survival, via IL-10 secretion [178]. These DLBCL Tfh cells were found to secrete IL-10 in vast amounts [178], and therefore might also influence T-cell activation and proliferation, since these can be inhibited by IL-10 [179]. Another subset of Tfh cells are follicular Tregs (Tfr). Compared to conventional Tregs, follicular Tregs (Tfr) have similar functions, are identified by CD4\(^+\)CXCR5\(^+\)Foxp3\(^+\), and may regulate follicular T helper cells (Tfh) and B-cells (reviewed in [180]). In DLBCL, Tfr cells are enriched [178]. Tfr cells were able to inhibit autologous T-cell proliferation and IFNy production and support tumor cell growth [165]. Additionally, in CLL, Tfh cells are involved. It has been shown that CLL proliferation is induced by CD40 ligand (CD40L) and IL-21 stimulation, of which the latter is produced by Tfh cells [181]. Furthermore, in FL, Tfh cells play an important role in supporting survival of the cancer cells. Upregulation of the IL-4, TNF, and CD40L pathways in Tfh cells, expression of CD40L on Tfh cells, as well as secretion of IL-4 and IL-21, and low secretion of IL-17 have been shown to support survival of FL cells [109,182–184]. IL-4 and CD40L signaling can lead to production of CCL17 and CCL22 by the malignant B-cells [183]. This, in turn, can again lead to migration of Tregs and IL-4 secreting T-cells, resulting in a self-sustaining positive feedback loop [183]. It thus seems that Tfh cells can promote lymphomas via direct support of the tumor cells as well as negatively influencing TIL and therefore may possibly influence the outcome of T-cell-based therapy.

4. Possible Solutions

The multiple levels of T-cell dysfunction that we describe here could serve as novel targets to improve the efficacy of T-cell-based therapies. Of the many approaches that have been described, we will focus on three possible solutions that could already be tested within clinical trials. The first is the addition of agents that target T-cells to improve their efficacy, the second is timing of autologous T-cell-based therapy and the third are specific solutions to improve CAR T efficacy either by adjusting the CAR T-cell design itself, or the CAR T cell production process.

4.1. Combination Therapy Improves ICB and BsAbs and Potentially CARs

Lenalidomide is an immunomodulatory drug that has been approved for treatment of multiple myeloma, MCL, and myelodysplastic syndromes. Lenalidomide was shown to bind to the E3 ubiquitin ligase cereblon, thereby inducing degradation of the transcription factors Aiolos and Ikaros [185,186]. Since Aiolos and Ikaros regulate T-cell fate, lenalidomide treatment induces skewing to a Th1 phenotype with enhanced expression of IL-2 and IFNy as well as inhibition of proliferation and functioning of Tregs [186–188]. In line with this, treatment with lenalidomide also had a positive effect on T-cells from patients with different B-cell malignancies. In CLL, FL and DLBCL, it has been shown that lenalidomide reverses dysfunctional synapse formation and improves CLL T-cell motility [151,157,189]. Furthermore, it has been shown that treatment of FL peripheral blood mononuclear cells (PBMCs) with lenalidomide resulted in enhanced activation, proliferation, and production of IFNy and IL-2 by T-cells upon TCR stimulation [190]. Additionally, avadomide, a cereblon E3 ligase modulator similar
to lenalidomide, improved T-cell responses in CLL via type I and II interferon signaling, eventually leading to responses in patient xenograft models with ICB [191].

Since T-cells from patients with B-cell malignancies might benefit from lenalidomide treatment, combination strategies involving T-cell therapy might therefore be feasible. These types of agents have already been tested in a clinical setting. For DLBCL, a phase II trial was started to evaluate the efficacy of CD19 CAR in combination with either lenalidomide or rituximab (NCT04002401). The studies on the combination of lenalidomide with either ICB or BsAbs in B-NHL are still limited but do seem to show enhanced effects [38–40,51]. Furthermore, reports have shown that for multiple myeloma, the addition of lenalidomide to BsAbs or ICB can be beneficial [192,193].

Results with lenalidomide combinations show that targeted drugs can potentiate T-cells and thereby improve T-cell-based therapy. However, due to toxicities, other options in addition to lenalidomide need to be considered. Idelalisib might be a feasible candidate. Especially for CLL, reports have been published regarding this phosphoinositide 3-kinase (PI3K) δ inhibitor. Recently, it has been shown that idelalisib inhibits IFNγ production and skews HD T-cells towards more effector differentiation upon stimulation [194]. In CLL, idelalisib is associated with a decreased amount of Tregs [189]. Furthermore, it led to a decrease in effector CD8+ T-cells together with decreased IFNγ production and degranulation in the Eμ-TCL1 mouse model [195]. Whether decreased Tregs and IFNγ production of T-cells in CLL are beneficial for T-cell mediated therapy still needs to be elucidated. Nevertheless, a phase II trial combining pembrolizumab and idelalisib in CLL is currently being conducted (ClinicalTrials.gov Identifier: NCT02332980). In DLBCL, PBMC stimulation in the presence of idelalisib also resulted in less production of IFNγ, but more IL-2 and a less differentiated phenotype as measured by CD27 and CD28 expression [196], which might be beneficial. Adoptive transfer of DLBCL-derived T-cells treated with idelalisib also showed increased in vivo persistence [196].

Additionally, ibrutinib has gained much interest with regard to its use in combination with autologous T-cell therapy. In addition to targeting BTK, ibrutinib also inhibits IL-2-inducible T-cell kinase (ITK) expressed by T-cells [197]. ITK inhibition by ibrutinib was shown to induce Th1 skewing in healthy donor T-cells [197]. However, it has previously been shown that ITK knockdown leads to increased Treg and Th1 differentiation [198,199], and ITK deficiency or inhibition decreased degranulation of CD8+ T-cells resulting in impaired cytotoxicity [200]. It thus seems that specific ITK inhibition may not lead to improved T-cell responses as seen upon ibrutinib treatment, and the observed improved T-cell function may be a subsequent result of decreased CLL function and presence induced by ibrutinib. Effects of ibrutinib on T-cells in B-cell malignancies have been well described for CLL. Ibrutinib induces Th1 skewing, together with CTLA-4 and PD-1 downregulation, a decreased Treg/CD4 ratio, and an increased T-cell receptor repertoire [197,201–203]. T-cells of CLL patients that had received prior ibrutinib had improved cytotoxic activity upon treatment with either a CD3xCD19 or CD3xROR1 BsAb, possibly due to enhanced synapse formation [59,62]. Efficacy of ICB might also be enhanced in combination with ibrutinib. In a Eμ-TCL1 CLL mouse model, it has been demonstrated that anti-PD-1 or PD-L1 in combination with ibrutinib led to increased tumor control [204]. In addition, in a mice xenograft MCL model, ibrutinib enhanced survival and ameliorated expression of exhaustion and inhibitory receptors on CAR T-cells [205]. Additionally, in a mouse lymphoma model, which was resistant to ibrutinib monotherapy, the combination of ibrutinib with anti-PD-L1 therapy significantly improved survival compared to anti-PD-L1 therapy alone [206]. Despite these promising results in a mouse model, results from a phase I/IIa study combining ibrutinib with nivolumab for CLL, FL and DLBCL were rather disappointing since the efficacy of the combination was comparable to monotherapy with either ibrutinib or nivolumab [41]. Similar results were obtained for FL and DLBCL upon combining ibrutinib with anti-PD-L1 antibody durvalumab [45].

Long-term treatment with ibrutinib, idelalisib or lenalidomide can lead to the development of severe adverse events [207,208]. Therefore, adequate timing and administering the correct dose of the specified therapy is important. For example, prior to starting T-cell-based therapy, patients might undergo induction with an immunomodulatory agent to restore T-cell dysfunction, which may boost
subsequent T-cell-based therapies in return. Unfortunately, to our knowledge, no (pre)clinical data are currently available that support the beneficial effects of differential timing of therapy to improve T-cell-based therapy.

In conclusion, T-cell modulatory agents are readily available and may be able to enhance T-cell therapy in a combination setting, in which timing could also play a role in the future. Lenalidomide trials, especially, indicate that they improve T-cell-based therapy, but future studies are needed to confirm this.

4.2. Consolidation Therapy

As discussed above, suppression of T-cell function can be the result of overwhelming numbers of tumor cells causing metabolic pressure in addition to restriction of T-cell function by expression of inhibitory ligands on tumor cells. Therefore, it may be beneficial to debulk tumor cells prior to T-cell-based therapies as it may create a window of opportunity in which T-cells recover (all or part of) their functions. This was perhaps unintentionally demonstrated in the first CAR T-cell trial where two patients who achieved CR after cytoreductive chemotherapy sustained that CR after subsequently receiving CAR T-cells [66]. Additionally, treatment of CLL patients with venetoclax and obinutuzumab not only led to eradication of the CLL, but also to reduced Tregs, Tfh and PD-1 expression on CD8+ T-cells, indicating a reversion of T-cell dysfunction and recovery of T-cell skewing [104]. Blinatumomab as consolidation after rituximab and chemotherapy in 28 DLBCL patients led to an ORR of 89% [52], which is slightly improved in comparison to R-CHOP alone [209], although it has to be awaited whether PFS increases upon addition of blinatumomab. These results indicate that T-cell therapy as a consolidation strategy might be a good alternative strategy to improve the outcome of patients. However, one of the difficulties of consolidation therapy is the timing of the treatments. T-cell-based therapies rely on the availability of the antigen and therefore may be applied as consolidation prior to reaching minimal residual disease negativity to achieve full efficacy.

4.3. Improving CAR T-Cell Therapy

Persistence and peak expansion of CAR T-cells are predictors of favorable clinical outcome and can greatly influence CAR T-cell efficacy [67,76,78,210]. Numerous methods to improve persistence and expansion are available and are currently investigated and focus primarily on increasing the numbers of memory T-cells. The phenotype of expanded CAR T-cell products in CLL patients had a more differentiated phenotype, becoming the most apparent after 20 days of culturing [211], and may impact the generated CAR T-cell product [76]. However, failure to generate adequate CAR T-cells could not be rescued by IL-2 or IL-7/IL-15 supplementation in CLL patients to levels to that of HD, implying that different methods to generate memory CAR T cells are necessary [211,212]. The phenotype of CARs generated from ALL patients were highly similar to CARs generated from HDs, which may explain why the clinical effectiveness of CAR T-cell therapy in ALL is high [213]. These results indicate that enhancing the memory phenotype of CAR T-cells may benefit efficacy of the therapy.

The type of costimulatory ligand in CAR can greatly impact CAR T cell function and phenotype. For example, differences in phenotype between 28z and BBz have been demonstrated in animal models, which show that the 4-1BB signaling domain enhanced CAR T-cell memory development and persistence, and promoted oxidative phosphorylation and mitochondrial biogenesis, while the CD28 signaling domain pushed towards an effector phenotype and glycolysis [214,215]. Selecting the correct co-stimulatory domain, or combining multiple co-stimulatory domains, may therefore improve CAR T cell function. Indeed, a combination of 4-1BB and inducible T cell co-stimulator (ICOS) into one CAR design greatly enhanced persistence and tumor eradication compared to either 4-1BB or ICOS alone in a mouse xenograft model bearing pancreatic tumors [216]. However, it may not be necessary to alter the CAR T cell design per se. Other methods exist to improve CAR T cell persistence and memory formation without altering the CAR T cell design itself.
The most evident method to obtain persisting CAR T cells may be through generating CAR T cells from a pool of purified memory T-cells. Wang et al. treated eight patients with first generation central memory-derived CAR T-cell infusions, and eight more patients received second generation central memory-derived 28z CAR T-cells [86]. The CR rate was 38% (three patients) for patients receiving first generation CAR T-cells, and the CR rate was 75% (six patients) for patients receiving a second generation CAR T-cell product [86]. Cytokines, metabolites, or inhibitors can be added during the generation of CAR T-cells to skew the T-cell composition towards a memory phenotype. For example, IL-15 added during CAR T-cell generation can preserve memory phenotype [210], although IL-15 supplementation on its own may not be enough to completely enhance CAR T cell efficacy [211,212]. In addition, metabolites such as L-arginine can also be added during culture. This has been shown to promote T-cell survival and oxidative phosphorylation and increase the percentage of central memory T-cells in a mouse model [217]. As a result, tumor-bearing mice injected with L-arginine-treated CAR T-cells had increased survival over the control group [217]. Additionally, the PI3K-inhibitor idelalisib can be added to CAR T-cells culture to enhance representation of naïve-like CD45RA+CCR7+ subset, and simultaneously reduce expression of inhibitory receptors PD-1 and TIM-3 [212]. Idelalisib could enhance the representation of memory-like T-cells in HD and CLL; however, the representation of memory-like T-cells in CLL in idelalisib-treated samples was still much lower compared to HD. Nevertheless, CAR T-cells generated with idelalisib slightly outperformed non-idelalisib cultured CAR T-cells in mice [212]. Improving memory formation can also be established by preventing lysosomal degradation of the CAR, after recognizing its cognate antigen [218]. Prevention of ubiquitination of CARs targeted for degradation in lysosomes not only improved the expression of surface CAR, but also increased the lysing capabilities of the CAR T-cells, absolute counts, and percentage of central memory T-cells [218]. Furthermore, the metabolic phenotype of these cells corresponded with that of memory T-cells, such as having improved oxygen consumption rate, maximum respiration, and spare respiratory capacity, which indicate enhanced oxidative phosphorylation and mitochondrial biogenesis [218]. These methods not only describe the many ways in which T-cells can be pushed towards a memory phenotype, but also demonstrate the increased CAR T efficacy as a result.

Preventing T-cell exhaustion either as a result of chronic stimulation, or indirectly induced by cancer cells, may improve CAR T-cell therapy as well. Overexpression of c-Jun, a component of the AP-1 transcription factor, can protect CAR T-cells from exhaustion and greatly enhance proliferation compared to a control CAR [219]. Additionally, overexpression of c-Jun greatly enhanced efficacy in solid tumors and improved survival in mice bearing osteosarcomas [219]. Alternatively, CAR T-cells can be equipped with a PD-1 dominant negative receptor to prevent signaling of exhaustion. Such CARs outperformed control CARs in a murine mesothelin mouse model [220]. Prevention of exhaustion may especially be beneficial in tumors where the PD-L1/PD-1 axis is important in tumor cell survival.

5. Conclusions

This review comprehensively shows that the efficacy of autologous-based T-cell therapy differs among B-NHL subtypes as well as per treatment modality. ICB has shown very discouraging results, and even in combination strategies, efficacy does not seem to improve and ICB is therefore likely not a feasible treatment modality in B-NHL including CLL. This is in contrast to BsAbs and CAR T-cells, which do elicit responses, although not to the extent of those observed in ALL. These diminished responses are likely due to different aspects of T-cell dysfunction that have been described in B-NHL subtypes. The recent advantages made in CAR T-cell production, and the development of immunomodulatory agents can be used to overcome T-cell dysfunction in these malignancies and improve T-cell mediated therapy for B-NHL.

Author Contributions: Conceptualization: A.W.J.M., J.A.C.v.B., S.H.T. and A.P.K.; writing—original draft preparation: A.W.J.M. and J.A.C.v.B.; writing—review and editing: A.W.J.M., J.A.C.v.B., S.H.T. and A.P.K. All authors have read and agreed to the published version of the manuscript.
**Funding:** A.P.K. is funded by a Dutch Research Council (NWO) VIDI grant and a European Research Council (ERC) consolidator grant.

**Conflicts of Interest:** A.P.K. receives research funding from Janssen, Abbvie, Roche/Genentech, Astra Zeneca, and Celgene and is a member of advisory boards of Janssen, Abbvie, Roche/Genetech, Juno.

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