Efficacy of Auto-CAR T Cell Therapy in Lymphoma

Subjects: Oncology

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While more than half of non-Hodgkin lymphomas (NHL) can be cured with modern frontline chemoimmunotherapy regimens, outcomes of relapsed and/or refractory (r/r) disease in subsequent lines remain poor, particularly if considered ineligible for hematopoietic stem cell transplantation. Hence, r/r NHLs represent a population with a high unmet medical need. This therapeutic gap has been partially filled by adoptive immunotherapy. CD19-directed autologous chimeric antigen receptor (auto-CAR) T cells have been transformative in the treatment of patients with r/r B cell malignancies.

Keywords: cellular therapy ; chimeric antigen receptor ; lymphoma

1. Introduction

Non-Hodgkin lymphomas (NHLs) account for 4% of all cancers and represent the seventh leading cause of cancer death in the United States [1] and eleventh worldwide [2]. Despite booming novel antineoplastic agent development, a significant number of NHL patients continue to succumb to their disease, experiencing rapidly progressive disease or early relapse.

Autologous CAR (auto-CAR) T cell therapy is an individualized technology that genetically modifies the patient's own T lymphocytes to specifically eradicate malignant cells and has drastically changed the landscape of many hematological malignancies, especially B cell NHLs. Key components of commercially available CAR T cell products consist of a CD-19 antigen-specific domain, a bridging transmembrane glycoprotein coupled to a costimulatory domain such as 4-1BB or CD28, which potentiates T cell activation signaling and improves CAR T cell expansion and persistence [3]. The process of CAR T cell therapy includes several steps: leukapheresis, ex vivo engineering and expansion of CAR T cells, and administration of a lymphodepleting conditioning regimen followed by infusion of the CAR T cell product.

2. Aggressive Lymphoma

2.1. Large B-Cell Lymphoma

Large B cell lymphoma (LBCL) is a heterogeneous group that includes several entities with variable molecular patterns and prognosis [4][5][6][7]. Frontline immunochemotherapy is curative for roughly two-thirds of LBCL patients [8]; however, those presenting with primary refractory disease or experiencing early relapse have a dismal prognosis, with only approximately a quarter of patients benefiting from subsequent lines of therapy [9][10].

- Pivotal clinical trials in ≥2 lines

Three pivotal single-arm early phase trials conducted in r/r adult LBCL patients who received at least two prior lines of systemic therapy, ZUMA-1 [11][12], JULIET [13][14], TRANSCEND [15][16], led to the registration of their respective CD19 auto-CAR product. Characteristics of the CAR T cell products and the safety and efficacy results of these trials are summarized in **Table 1**.

Table 1. Characteristics and results of pivotal clinical trials for CD 19 auto-CAR T cell therapies approved in relapsed/refractory B cell lymphoma.

Variable	ZUMA-1 NCT02348216	JULIET NCT02445248	TRANSCEND NCT02631044	ZUMA-2 NCT02601313	ZUMA-5 [1] NCT03105336
Auto-CAR product	Axi-cel	Tisa-cel	Liso-cel	Brexu-cel	Axi-cel
Histologic type (%)	DLBCL (76), PMBL (8), tFL (16)	DLBCL (80), HGBL (15), tFL (18), Other (2)	DLBCL (51), HGBL (13), FL grade 3b (1), PMBL (6), tFL (22), tiNHL (7)	MCL	iNHL, including FL (84) and MZL (16)

Variable	ZUMA-1 NCT02348216	JULIET NCT02445248	TRANSCEND NCT02631044	ZUMA-2 NCT02601313	ZUMA-5 [1] NCT03105336
Enrolled patients–no/Infused patients–no (%)	111/101 (91)	165/115 (69)	344/269 (85) [2]	74/58 (92)	127/124 (98)
Median age, yr (range)	58 (23–76)	56 (27–76)	63 (18–86)	65 (38–19)	60 (34–79)
Bridging therapy (%patients)	Corticosteroids (NA)	Chemotherapy (93)	Chemotherapy (59)	Any (35)	Any (4)
Median prior lines of therapy (range)	3 (2–4)	3 (1–6)	3 (1–8)	3 (1–5) [3]	3 (2–4) [4]
Best overall response rate (%)	74	53	73	91	94
Complete response rate (%)	54	39	53	68	79
Median follow-up (mo)	51.1	40.3	29.3	35.6	30.9
Median duration of response (mo)	11.1	NE	23.1	38.6	NR
Median progression-free survival (mo)	5.9	2.9	6.8	39.6	NR
Progression-free survival at 24 mo (%)	40	35	40.6	52.9	65.6 (18 mo)
Progression-free survival among patients with CR at 24 mo (%)	70	80	49.5	71.8	NR
Median overall survival (mo)	25.8	11.1	27.3	NR	NR
Overall survival at 24 mo (%)	44 (48 mo)	45	50.5	~84	88 (18 mo)
Adverse Events grade ≥3 (%)	98	89	79	99	85
Serious Adverse Events(%)	48	65	45	68	46
Adverse Events of special interest					
Cytokine release syndrome (CRS) [5]					
All (%)	92	58	42	91	78
Grade ≥3 (%)	11	17	2	15	6
Tocilizumab	43 [7]	24	18 [8]	59	50 (all iNHL)
Corticosteroids (%)	27 [7]	16	2	22	18 (all iNHL)
Vasopressors (%)	13	10	3	16	5 (all iNHL)
Neurological events [6]					
All (%)	67	20	30	63	56
Grade ≥3 (%)	32 [7]	11	10	31	15
Tocilizumab	43 [7]	20	NA	26	36
Corticosteroids (%)	27	12	NA	38	6
Infections grade ≥ 3 (%)	28	19	12	32	18 (all iNHL)

Variable	ZUMA-1 NCT02348216	JULIET NCT02445248	TRANSCEND NCT02631044	ZUMA-2 NCT02601313	ZUMA-5 [1] NCT03105336
Late cytopenia grade ≥ 3 [9] (%)	38	32	37	26	33
Immunoglobulin (%)	31	33	21	32	9 (all iNHL)

Note: The purpose of this table is to summarize currently available data. Head-to-head studies have not been performed, and no comparisons can be made. [1] Results for the FL group if not indicated as iNHL. [2] Twenty-five patients received a product that failed to meet specifications but was deemed safe to administer. [3] Patients must be exposed to anthracyclines- or bendamustine-containing regimen, anti-CD20 and BTKi. [4] Patients must be exposed to prior anti-CD20 and alkylating agents. [5] Cytokine release syndrome in this table are all graded according to Lee scale criteria, even though CRS in JULIET was initially reported according to Penn grading scale. [6] Neurological events reported according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.03). [7] Received for either CRS and/or ICANS. [8] Tocilizumab alone was given to 10% of patients. [9] Cytopenias ≥ 28 days in JULIET, ≥30 days in the other studies. Abbreviations: Axi-cel (axicabtagene ciloleucel); Be, bendamustine; brexu-cel (Brexucabtagene autoleucel); BTKi, bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; Cy, cyclophosphamide; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; Flu, fludarabine; HGBL, high-grade B cell lymphoma; iNHL, indolent non-Hodgkin lymphoma; liso-cel (Lisocabtagene maraleucel); LBCL, large B cell lymphomas; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not available or reported; NE, not estimated; NR, not reached; PMBL, primary mediastinal b cell lymphoma; tFL, transformed follicular lymphoma; tiNHL, transformed indolent non-Hodgkin lymphoma; tisa-cel (tisagenlecleucel).

All trials included a relatively similar proportion of advanced-stage patients with a comparable median of prior lines; however, some distinctions in patient selection have to be highlighted. Notably, TRANSCEND included a higher proportion of patients above 65 years (41%) compared to ZUMA-1 (24%) and JULIET (23%), whereas the latter included more patients relapsing after autologous stem cell transplantation (49%) compared to 21% of patients in ZUMA-1 and 33% in TRANSCEND. The percentage of high-grade B cell lymphoma with MYC rearrangement was, respectively, 6%, 17% and 13% in ZUMA-1, JULIET and TRANSCEND. On the other hand, the number of primary refractory patients was higher in ZUMA-1 (98%) versus 55% in JULIET and 67% in TRANSCEND. Furthermore, trials differed in the inclusion of histologic subtype, with primary mediastinal B cell lymphoma (PMBL) only included in ZUMA-1 and TRANSCEND, and inpatient access to bridging therapy (BT) which was only permitted in JULIET and TRANSCEND. Finally, the proportion of “infused/enrolled” patients was significantly different across trials, respectively 91%, 69% and 85% for ZUMA-1, JULIET and TRANSCEND, with a significantly higher drop-out rate seen in JULIET, likely due to an extended time from leukapheresis to auto-CAR delivery for tisa-cel (54 days). Manufacturing time has been recognized as being of paramount importance in this r/r setting, as patients may experience a rapid progression of their disease whilst awaiting the auto-CAR product.

Taken together, these differences make pivotal cross-trial comparison difficult. However, all trials yielded remarkable overall response rates (ORR) ranging from 53% to 74%, with complete response (CR) reached in 39% to 54% of patients. Moreover, 65% to 80% of responders were able to maintain their remission with long-term follow-up. Long-term progression-free survival (PFS) and overall survival (OS) rates are summarized in **Table 1** [12][14][16]. In their 4-year updated analysis of ZUMA-1, Jacobson et al. reported a strong correlation between event-free survival (EFS) and OS, and suggest to use EFS as a surrogate end-point for future trial design [12]. Several studies have attempted to indirectly compare outcomes of pivotal trials, adjusting for variables such as baseline characteristics, BT, and time to leukapheresis, but heterogeneity in the study design and limitations of data availability make it difficult to draw any conclusions, and head-to-head trials are needed [17][18][19][20]. A range of factors may affect CAR-T cell therapy efficacy, including patient and disease characteristics, CAR-T cell manufacturing and the type and depth of lymphodepletion. Attempts to identify molecular biomarkers of response to CAR T cell therapy (e.g., tumour expression of CD19, CD3, PD-1, PD-L1, CD3, TIM3 and LAG3) have so far been disappointing [13]; however, in the era of precision medicine, identifying patients more likely to respond to adoptive T-cell therapy and improving prognostic predictions is of paramount importance and should be prioritized for future trials.

Adverse events (AE) grade ≥3 were seen in 79–98% of patients, including 12–28% grade ≥3 infections. All grade cytokine release syndrome (CRS), as graded by Lee criteria [21], occurred in 42% to 92% of patients, including 2–11% of grade ≥3 CRS. Tocilizumab, corticosteroids and vasopressors were administered in 18–43%, 2–27% and 3–13% of cases, respectively. All grade neurological events, nowadays known as immune effector cell-associated neurotoxicity syndrome (ICANS), occurred in 30–67% of patients, with 10–32% reported as grade ≥3. Late cytopenias grade ≥3 were observed in

32–38%; immunoglobulin supplementation was necessary in 21–31% of cases. No new safety signals were reported with extended follow-up.

- Real-world evidence and outpatient setting

Several hundreds of patients have now been treated with auto-CAR T cells worldwide. Multiple groups retrospectively assessed the real-world outcomes and confirmed the feasibility and safety of this strategy [22][23][24][25][26][27][28][29][30][31][32] 8 August 2022 12:13:00 PM. Overall, patients treated in the standard of care setting tended to be older, with a third to half over the age of 65 years, and had a lower performance status and more advanced disease with a higher International Prognostic Index (IPI) score; approximatively half of these patients would not have been eligible for pivotal trials. Some real-world cohorts also reported a higher proportion of high-grade B cell lymphoma with MYC rearrangements [23][24][25]. Additionally, 53% to 84% of patients received BT, a factor shown to be predictive of reduced survival in retrospective analyses [33][34] and that may reflect a higher tumor burden and/or more aggressive disease at baseline.

Except from the UK experience [30], efficacy was surprisingly not impacted by less stringent patient selection; the best ORR ranged from 64% to 70% for axi-cel [22][23][25][27][30] and 46% to 62% for tisa-cel [24][25][27][28][29][30]. CR rates also remained consistent, ranging from 52% to 64% for axi-cel [22][23][25][27][29][30] and 38% to 44% for tisa-cel [24][25][28][29][30]. As previously demonstrated in pivotal studies, durability of response was sustained in complete responders. Approximately 10% of patients did not receive CAR infusion, either because of rapidly progressive disease or manufacturing failures (2–3%). Leukapheresis-to-infusion time was shorter for axi-cel (21 to 38 days) [22][23][25][27][29][30] than tisa-cel (32 to 46 days) [24][25][27][28][29][30]. Due to its later approval, such “real-world” data are presently lacking for liso-cel. Real-world safety results were consistent with those obtained in clinical trials, confirming a specific but manageable toxicity profile, with a tendency to a lower severe AE rate compared to pivotal trials, a finding potentially explained by increasing experience with CAR T cell toxicity management and earlier use of tocilizumab [35][36][37].

Finally, the OUTREACH multicenter phase 2 trial investigated the feasibility of liso-cel in the outpatient setting. The outcomes and safety of 52 patients receiving CAR T cell therapy as outpatients and monitored in non-university medical centers have recently been reported as similar to that in the inpatient setting. Of importance, nearly one-third of patients in this study did not require hospitalization [38].

- Randomized clinical trials in earlier lines of therapy

Based on the outstanding results of pivotal trials, axi-cel, tisa-cel and liso-cel were tested against standard of care salvage chemotherapy followed by autologous stem cell transplantation (SOC) in three large multicenter phase 3 randomized trials, respectively: ZUMA-7 [39], BELINDA [40] and TRANSFORM [41]. Eligible patients had to have progressive disease or relapse within 12 months from initial immunochemotherapy completion. All trials evaluated EFS as a primary end-point, although the definition of EFS slightly varied from one trial to another, with ZUMA-7 and TRANSFORM including the start of a new treatment line as an event (**Table 2**). Contrary to BELINDA and TRANSFORM, ZUMA-7 did not permit patients to cross over to the CAR T arm. No new safety signals were reported across trials.

Table 2. Characteristics and results of CD19 auto-CAR arm in randomized phase 3 trials in relapse/refractory B cell lymphoma ≥ 1 line of therapy.

Variable	ZUMA-7 NCT03391466	BELINDA NCT03391466	TRANSFORM NCT03575351
CAR product	**Axi-cel**	**Tisa-cel**	**Liso-cel**
Primary end-point definition (Event-free survival)	**SD or PD up to day 150, new lymphoma treatment, death**	**SD or PD disease at week 12, death**	**SD or PD at week 9, new lymphoma treatment, death**
Crossover (%)	**Not permitted**	**Allowed (51)**	**Allowed (55)**
Manufacturing success (%)	**100**	**97**	**99**
Lymphodepleting regimen	**Flu 30 mg/m^2 + Cy 500 mg/m^2 daily × 3 days**	**Flu 25 mg/m^2 + Cy 250 mg/m^2 daily × 3 days [1]**	**Flu 30 mg/m^2 + Cy 300 mg/m^2 daily × 3 days**
Enrolled patients–no (assigned to CAR)	**359 (180)**	**322 (162)**	**182 (92)**
CAR-infused patients–no (%)	**170 (94)**	**155 (96)**	**89 (97) [2]**

Variable	ZUMA-7 NCT03391466	BELINDA NCT03391466	TRANSFORM NCT03575351
Median time to infusion (days)	13	52	36
Bridging therapy (%)	Corticosteroids only (36)	Chemotherapy (83)	Chemotherapy (63)
Histologic type (%)			
DLBCL (ABC subtype)	70 (9)	62 (32)	58 (23)
HGBL	17	24	24
PMBL	-	7	9
FL grade 3b	-	3	1
tiNHL	11	17	8
Other	13	3	1
Secondary CNS involvement	-	3	-
Median age, yr	58 (range 21–80)	59.5 (range 19–79)	60 (IQR 54–68)
Secondary IPI score ≥ 2 (%)	46	65	40
Refractory disease [3,4] (%)	74	66	45
Best overall response rate (%)	83	46	86
Complete response rate (%)	65	28	66
Median progression-free survival (mo)	14.5	NA	14.8
Progression-free survival (%)	~46 (24 mo)	NA	52 (12 mo)
Median event-free survival (mo)	8.3	3	10.1
Event-free survival (%)	40.5 (24 mo)	NA	45 (12 mo)
Median overall survival (mo)	NR	NR	NR
Overall survival at 24 months (%)	~61 (24 mo)	NA	~79 (12 mo)
Median follow-up (mo)	25	10	6.2
Adverse Event grade ≥ 3 (%)	91	84	92
Serious Adverse Events (%)	50	36	48
Adverse Events of special interest			
Cytokine release syndrome			
All (%)	92	61	49
Grade ≥ 3 (%)	6	5	1
Tocilizumab	64	52	23 [5]
Corticosteroids (%)	24	17	-
Vasopressors (%)	6	NA	-
Neurological events [6]			
All (%)	60	10	12
Grade ≥ 3 (%)	21	2	4
Corticosteroids (%)	32	NA	8 [7]
Infections grade ≥ 3	14	NA	15

Variable	ZUMA-7 NCT03391466	BELINDA NCT03391466	TRANSFORM NCT03575351
Cytopenia grade ≥ 3 (>30 days) [8]	29	NA	43

Note: The purpose of this table is to summarize data. Head-to-head studies have not been performed and no comparisons can be made. [1] If contraindicated bendamustine 90 mg/m^2 for 2 days. [2] One patient received a nonconforming CAR product. [3] Refractory disease defined as a lack of complete response to first-line therapy. [4] Cytokine release syndrom graded according to Lee scale criteria. [5] 13% associated to corticosteroids. [6] Neurological events reported according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE versio n 4.03). [7] 1% associated with tocilizumab. [8] Defined as >30 days persistent grade ≥ 3 cytopenia. Abbreviations: Axi-cel (axicabtagene ciloleucel); Be, bendamustine; brexu-cel (Brexucabtagene autoleucel); BTKi, bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CNS, central nervous system; Cy, cyclophosphamide; d, day; DLBCL, diffuse large b-cell lymphoma; FL, follicular lymphoma; Flu, fludarabine; HGBL, high-grade B-cell lymphoma; IPI, international prognostic index; iNHL, indolent non-hodgkin lymphoma; liso-cel (Lisocabtagene maraleucel); LBCL, large B-cell lymphomas; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not available; NR, not reached; PMBL, primary mediastinal b-cell lymphoma; tFL, transformed follicular lymphoma; tiNHL, transformed indolent non-hodgkin lymphoma; tisa-cel (tisagenlecleucel); yr, year.

Two of these trials demonstrated the superiority of CD 19 auto-CAR T cell therapy over SOC: ZUMA-7 and TRANSFORM, whereas BELINDA failed to meet its primary end-point. Overall, baseline patient characteristics (age, disease stage, ECOG) were similar compared to prior pivotal trials (**Table 2**). ORR and CR rates were 83% and 65%, 46% and 28%, and 86% and 66% for ZUMA-7, BELINDA and TRANSFORM, respectively. EFS was significantly longer for axi-cel (HR 0.40, $p < 0.0001$) and liso-cel (HR, 0.35; $p < 0.0001$), while tisa-cel did not perform better than SOC (HR, 1.07; $p = 0.61$). Median EFS was 8.3, 3 and 10.1 months for axi-cel, tisa-cel and liso-cel versus 2, 3 and 2.3 months for SOC, respectively. Results for SOC were comparable to those reported in the literature [9][42][43], with only 35%, 33% and 46% of patients proceeding to autologous stem transplantation in each trial, respectively. Interestingly, quality of life assessed by patient-reported outcomes also favored axi-cel and liso-cel CAR T cells over SOC [44][45].

A few differences may have contributed to these discrepant results between studies: ZUMA-7 had the most stringent study design, with no BT permitted except for corticosteroids, thereby potentially excluding patients with high tumor burden and/or rapidly progressive disease. By contrast, most patients on TRANSFORM (63%) and BELINDA (83%) received BT, including 12% of patients receiving two different regimens of BT in the latter, potentially reflecting a population with a higher disease burden. Additionally, the median time to infusion was again longer for tisa-cel (52 days). Whether these differences have an impact on outcomes remains unclear as no direct prospective comparison of these CAR T cell products is yet available.

- Primary and secondary CNS involvement

TRANSCEND was the only pivotal trial to allow patients with secondary CNS involvement (SCNSL), accounting for only 3% (N = 7) of patients. Small retrospective series evaluated outcomes of axi-cel and tisa-cel in SCNSL patients in the real-world setting [46][47][48] and were recently summarized in a systematic review (N = 44) [49]. No additional neurologic AEs were reported, and response rates seem similar to patients without CNS involvement, whereas the duration of response appears less sustained, although small patient numbers may limit the interpretability of results. Even though these findings require prospective confirmation, they confirmed the feasibility of CAR T cell therapy in this setting. Likewise, Frigault et al. recently reported the outcomes of 12 primary CNS lymphoma (PCNSL) patients treated with tisa-cel (NCT02445248), of which 6 achieved CR and maintained their remission at 1 year of follow-up [50]. Feasibility and safety were also confirmed by another group in 5 PCNSL patients [51]. The utility of liso-cel in PCNSL is currently being investigated in TRANSCEND WORLD (NCT03484702).

2.2. Mantle Cell Lymphoma (MCL)

Two recent multicenter trials have shown clear clinical benefits from brexucabtagene autoleucel (brexu-cel) and liso-cel in r/r MCL. ZUMA-2 enrolled 74 patients with heavily pretreated r/r MCL, the vast majority failing or relapsing after BTKi [52]. The impressive ORR of 85% and CR of 59% seen in the intention-to-treat analysis led to FDA approval of brexu-cel for this indication (**Table 1** and **Table 2**). Minimal residual disease (MRD), assessed by clonoSEQ (10^{-6} level), was undetectable in 79% of evaluable patients (N = 19) at 6 months and sustained after 3 years of follow-up. The benefit was seen across all high-risk subgroups, including BTKI refractoriness, high MIPI score, early progressors (POD24) and

elevated Ki67 ≥ 50%. Due to the small number of patients, no conclusions could be made for TP53 mutated and blastoid variants, but these may have a less favorable outcome. Similarly, the first results of the MCL TRANSCEND cohort (N = 32) do compare favorably, with an ORR of 84% and over half of patients in CR [53].

Preliminary real-world data of two multicenter groups have also emerged, one from the U.S. and one from Europe [54][55], both reproducing safety and efficacy results of ZUMA-2 with the best ORR and CR rates in the range of 86–91% and 64–79%, respectively. In the U.S. study, the 3-month PFS rate was 80.6%, and the 6-month OS rate was 82.1% [54], while the 12-month PFS and OS rates of the European study were 76% and 61%, respectively [55]. Manufacturing failures occurred in 6–8% of cases, and 65–82% of patients received BT compared to 32% in ZUMA-2. Finally, an ongoing clinical trial is exploring the efficacy of tisa-cel in combination with ibrutinib in patients with r/r MCL (TARMAC, NCT04234061). Even though it is too early to draw conclusions on the curative potential of CAR T cells in this setting, this modality offers durable responses in over half of this poor-prognosis population.

2.3. T-Cell Lymphoma

T-cell lymphoproliferative disorders constitute a highly heterogenous group of lymphomas related to poor outcomes and an unmet need for r/r patients or ineligible for transplantation. The applicability of CAR T cell therapy in T cell lymphoma is much more challenging; limitations have been well-described by Safarzadeh et al. in their recent review and include the lack of T-cell tumor-specific targetable antigens (CD3, CD5, CD7) with an inherent risk of CAR T-mediated T-cell aplasia, CAR T cell fratricide resulting in poor CAR T persistence and the risk of malignant T cell contamination during leukapheresis resulting in a malignant auto-CAR construct, among others [56]. A recent phase 1 study reported a promising safety profile and high response rates (19/20 CR in the bone marrow by day 28, 5/9 extramedullary CR) with a CD7-targeted CAR in 20 patients with r/r T-cell acute lymphoblastic leukemia/lymphoma [57]. Other ongoing early phase trials are currently evaluating the safety and efficacy profile of CAR T cells directed against CD7 (NCT04840875, NCT04689659, NCT04480788, NCT05059912, NCT04599556, NCT03690011, NCT04823091), CD5 targeted CAR T (NCT04594135, NCT03081910, NCT05138458) and CD4-targeted CAR (NCT03829540). Other CAR modalities, such as allogeneic T and NK CAR constructs, are also under investigation (NCT04984356, NCT02742727).

3. Indolent Lymphoma

Despite significant improvements in the armamentarium of novel therapeutic strategies within the past decade, most indolent lymphomas remain incurable, with the exception of rare patients eligible for allogeneic stem cell transplantation (allo-SCT) [58]. Indolent lymphomas are highly heterogeneous [59], with certain subgroups having high-risk clinical and molecular features that may result in a more aggressive disease course and significantly reduced survival [60]. These patients also tend to have shorter response duration with subsequent lines of therapies, and thus, the management of patients who develop acquired resistance remains challenging [61].

3.1. Follicular Lymphoma and Marginal Zone Lymphoma

The efficacy of CAR T cells was first demonstrated in a heavily pretreated advanced-stage FL patient in 2010 [62], and this was followed by a small case series [63][64]. Axi-cel has been recently approved by the FDA in this setting based on interim results of ZUMA-5, evaluating the benefit of axi-cel in r/r indolent lymphoma [65]. This phase 2 trial enrolled 124 FL and 16 marginal zone lymphoma patients. Among the 80 evaluable FL patients, 94% responded, including 79% of CR. With 31 months of follow-up, the 18-month PFS and OS rates were 65.6% and 88%, respectively [66]. These results also compare favorably to the outcomes of a retrospective multicenter cohort treated with standard immunochemotherapy [67]. Tisa-cel has also been evaluated in high-risk FL. With a median follow-up of 17 months, 69% of the 97 patients infused in the ELARA study achieved a CR, with an ORR of 86% [68]. At the time of writing, no results of the TRANSCEND FL cohort have so far been published.

3.2. Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Early reports described the preliminary activity of CAR T cell therapy in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), either as monotherapy or in combination with BTKi [69][70][71][72][73]. TRANSCEND CLL-004 is a Phase 1 study that enrolled 22 patients withr/r CLL/SLL who were treated with liso-cel. Half of patients were refractory to both BTKi and BCL2i, 83% had high-risk genetic features. ORR and CR rates were 82% and 45%, respectively. In the 20 evaluable subjects, MRD was undetectable in 75% and 65% in the blood and bone marrow, respectively [74]. Liso-cel and ibrutinib in combination were deemed safe and tested in 19 r/r CLL/SLL patients. ORR and CR/CRi were 98% and 48% at one month post-CAR infusion. MRD negativity was 89% in the blood and 79% in the bone marrow, assessed, respectively, by flow cytometry and next-generation sequencing (10–4 level) [75]. The ongoing ZUMA-8 Phase 1/2 trial is

currently investigating the role of brexu-cel in this setting [76]. Additionally, promising activity has also been described in patients with transformed CLL/SLL (Richter syndrome) [70][77][78][79].

4. Hodgkin Lymphoma

CAR T cell development in Hodgkin Lymphoma has so far been less promising than in B cell NHL [80]; however, Ramos et al. recently demonstrated encouraging safety and efficacy results using a fludarabine-based lymphodeleting regimen in 41 heavily pretreated HL patients with 7 median prior lines of therapy [81]. Among the 32 evaluable patients, ORR was 72%, and 59% of patients achieved CR; 1-year PFS and OS were 36% and 94%, respectively. CD30 CAR T has also been evaluated in combination with a PD1 inhibitor in a Phase 2 trial conducted in 12 CD30 positive lymphoma patients (9 HL, 2 grey zone and 1 angioimmunoblastic lymphoma) with some durable responses [82].

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