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REVIEW

Clinical Insights on Brexucabtagene Autoleucel for the Treatment of Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

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Abstract: Autologous chimeric antigen receptor-modified T-cell therapy (CAR-T) has revolutionized treatment paradigms across multiple lymphoid malignancies, including relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL). The introduction of the CD19-directed CAR-T product brexucabtagene autoleucel (brexu-cel; Tecartus) in October 2021 made this treatment approach available for the first time for adults with R/R B-ALL, a historically challenging clinical entity to treat. In this review, we will discuss the pivotal clinical trial data from the ZUMA-3 study that led to the US Food and Drug Administration (FDA) approval of brexu-cel, including clinical outcomes and key toxicity data (most importantly, the incidence and severity of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome). Additionally, we will compare and contrast these data from the ZUMA-3 study with "real-world" data from examinations of patient outcomes with brexu-cel as an FDA-approved therapy in R/R B-ALL, and discuss practical considerations with brexu-cel use in the clinic, including the role of consolidative allografting for patients post-brexu-cel. We finish by discussing future directions for CAR-T use in R/R B-ALL with the anticipated introduction of a new CD19-directed CAR-T product – obecabtagene autoleucel – in the near future.

Keywords: brexucabtagene autoleucel, acute lymphoblastic leukemia, adults, chimeric antigen receptor, cellular immunotherapy

Background

Chimeric antigen receptor-modified T-cell therapy (CAR-T) has altered the treatment landscape for several lymphoid malignancies, including B-cell acute lymphoblastic leukemia (B-ALL). While historically disease relapse following frontline chemotherapy portended a dismal prognosis,[1,2] the introduction of novel immunotherapies including CD19-directed CAR-T has fundamentally changed the prospects for patients who find themselves in this situation. The first-ever approved CAR-T product was tisagenlecleucel (tisa-cel; Kymriah), a CD19-directed CAR-T for children, adolescents, and young adults (AYA) ≤25 years old with relapsed/refractory (R/R) B-ALL, based upon results of the pivotal Phase I/II ELIANA study.[3] While not the focus of this review, tisa-cel bears brief discussion given the historic significance of this of this agent, specifically that it was the first CAR-T agent commercially available in R/R B-ALL. The tisa-cel CAR-T construct employs a 4–1BB costimulatory domain – typically associated with slower in-vivo expansion kinetics as compared to CAR-T products bearing the CD28 costimulatory domain, which are associated with more rapid in-vivo expansion.[4] On the ELIANA study, eligible patients included adults up to the age of 21 *at the time of initial diagnosis* with CD19+ R/R B-ALL; no prior receipt of anti-CD19 therapy was permitted. The primary endpoint was morphologic complete remission (CR; <5% bone marrow blasts) or complete remission with incomplete hematologic recovery (CRi) within 3 months of tisa-cel treatment. Ninety-two patients were enrolled, and 75 patients were ultimately treated with tisa-cel after receiving lymphodepleting chemotherapy with fludarabine and cyclophosphamide (flu/cy). Among patients treated with tisa-cel, the CR/CRi rate at 3 months was 81%, all of whom were negative for measurable residual disease (MRD) by multiparameter flow cytometry (MFC; 100% MRD-). Any grade cytokine release syndrome (CRS) occurred in 77% of patients and immune effector cell-associated neurotoxicity syndrome (ICANS) of any grade occurred in 40% of patients.

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Whereas tisa-cel is a 4-1BB costimulatory domain-based CAR-T product, brexucabtagene autoleucel (brexu-cel; Tecartus) is CD28-based. This CAR-T product is currently approved in the United States, European Union, and other jurisdictions for R/R B-ALL[5] as well as mantle cell lymphoma (MCL).[6] Brexu-cel, in essence, is the same CAR-T product as axicabtagene autoleucel (axi-cel; Yescarta, approved for R/R B-cell non-Hodgkin lymphomas[7]), although brexu-cel undergoes an additional processing step to remove any circulating blasts harvested during the initial leukapheresis procedure, thereby reducing the potential for activation and T-cell exhaustion during the ex-vivo manufacturing process.[5] Brexu-cel was FDA-approved in October 2021 for use in adults >18 years old with R/R B-ALL based upon the results of the pivotal ZUMA-3 study.[5,8] Since its FDA approval, brexu-cel has been the primary CAR-T product used in adult ALL. With emerging real-world data highlighting its performance as a commercial therapy, as well as a different CD19 CAR-T product on the horizon in this disease space, we believe a review of brexu-cel in ALL is particularly timely.

Initial Findings with Brexucabtagene Autoleucel

The ZUMA-3 study was a multicenter, open-label, single-arm phase I/II study investigating brexu-cel use in R/R B-ALL. Eligible patients were >18 years old with R/R disease defined as primary refractory, first relapse with <12 months of an initial remission duration, or ≥2 lines of prior therapy; with evaluable morphologic bone marrow disease (>5% marrow blasts); and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Prior allogeneic hematopoietic cell transplant (HCT) and blinatumomab were permitted (the latter if CD19 expression was retained on >90% of leukemic blasts). Patients with serious, active infections; active graft-versus-host disease; or overt central nervous system (CNS) involvement (CNS-2 or CNS-3 disease) were excluded. Patients received flu/cy lymphodepleting chemotherapy, specifically with a fludarabine dose of 25mg/m^2 IV on Days −4, −3, and −2, and cyclophosphamide 900mg/m^2 IV on Day −2. Patients then received 1×10^6 CAR-T cells/kg on Day 0 (patients with a body weight of >100 kg received a flat dose of 1×10^8 CAR-T cells). The primary endpoint was the rate of morphologic CR/CRi by central assessment; secondary endpoints included duration of remission (DOR), overall survival (OS), relapse-free survival (RFS), and MRD-negativity rate by MFC.

A total of 71 patients enrolled over a 1-year period between October 2018 and October 2019 and underwent leukapheresis. Brexu-cel was successful manufactured and administered to 55 patients (77%). Manufacturing time from leukapheresis to product release was around 2 weeks both for patients in the US and in Europe. During this time, bridging therapy was recommended for patients with a higher disease burden (defined as >25% marrow blasts or >1000 blasts/μL in blood), which could be chosen by the treating physician from a list of predetermined chemotherapy-based options. In total, 91% of infused patients (n = 51) received bridging therapy. Sixteen patients ultimately did not receive brexu-cel for a variety of factors, including intervening adverse events, manufacturing failures, withdrawal of consent, loss of eligibility, or other factors.

Among the infused patients (n=55; efficacy population), the median age was 40 (interquartile range [IQR]: 28–52); 45% had received prior blinatumomab; 22% had received prior inotuzumab ozogamicin; and 42% had received prior HCT. In the efficacy cohort of treated patients (n=55), the morphologic CR/CRi rate was 71%; 97% of the responders (and 76% of all treated patients) were MRD- by MFC. Among all trial enrollees (n=71), the intention-to-treat (ITT) CR/CRi rate was 55%. Eighteen percent of patients (n=10) received consolidative HCT following brexu-cel treatment. With a median follow-up of 16.4 months, median OS was 18.2 months, median RFS was 11.6 months, and the median DOR was 12.8 months. Any-grade CRS occurred in 89% of patients, and grade 3+ CRS occurred in 24% of patients; any-grade ICANS occurred in 60% of patients, and grade 3+ ICANS occurred in 26% of patients (including 1 grade 5 event). Tocilizumab was given to 80% of patients experiencing CRS and/or ICANS, and steroids were given to 75% of such patients.

Long-Term Follow-Up with Brexu-Cel

Since the initial report of the ZUMA-3 trial, there have been several notable follow-up and post-hoc analyses. One feature in some of these reports is the inclusion of the 45 patients treated in the Phase I portion of the trial.[8] While still being treated with the same product, some of these patients received different cell doses (ie, 1 of 3 dose levels ranging between $0.5–2\times10^6$ cells/kg). They were also managed according to two different adverse event management strategies,

with a revision to introduce corticosteroids earlier in the management of ICANS and reserve tocilizumab only for treatment of CRS. This revised strategy was carried forward into the Phase II portion, so it reflects how the bulk of patients treated with this investigational product were managed. Nonetheless, one must keep these differences in mind when interpreting data from these pooled phase I + II follow-up analyses of the ZUMA-3 study.

With that context, there is now over 4 years of follow-up for the 78 patients who received the pivotal dose (ie, 1×10^6 cells/kg) in the phase I or II portion of ZUMA-3.[9] From this, the median OS for all treated patients was 25.6 months (95% confidence interval [CI]: 16.2–60.4 months). When restricted to the patients who achieved CR/CRi, this increased to an impressive 47 months (95% CI: 23.2 months – not estimable). This study also found numerically longer survival among patients under age 26 and those with no prior blinatumomab, with only 1 prior line of therapy, and who did not proceed to subsequent allogeneic HCT, though caution was raised about drawing conclusions from these small, unbalanced subgroups. This long-term follow-up analysis also reported a relatively under-described outcome of CAR-T trials that is more germane to studies of HCT: non-relapse mortality (NRM). Notably, the rate of NRM at 4 years was 25% (95% CI: 15–37%), with only 6 of 17 NRM events observed in patients who received subsequent HCT. Specific causes of these non-relapse deaths were not provided.

Previous follow-up reports from ZUMA-3 have made other interesting observations. For example, at 2 years of follow-up, a comparison to an external set of controls (SCHOLAR-3) was performed.[10] This synthetic control arm (SCA) was generated from patient-level data from historical clinical trials of alternative therapies for adults with R/R B-ALL; such patients would have received blinatumomab, inotuzumab ozogamicin, or standard chemotherapy.[11] Propensity-score matching was applied to identify comparable patients in both groups using their baseline characteristics. From these subsets, outcomes for patients on ZUMA-3 (n = 49) were significantly better than those in the SCA (n = 40): OS was 25.4 months vs 5.5 months (hazard ratio [HR] 0.32, $p < 0.001$), respectively.

While provocative, these findings from the comparison of ZUMA-3 to SCHOLAR-3 are difficult to contextualize in the current treatment landscape of B-ALL. There is unlikely to ever be a randomized controlled trial of CAR-T vs chemotherapy in this setting, since it is known that chemotherapy is inferior to both blinatumomab and inotuzumab ozogamicin. Propensity-score matching is one method to artificially generate head-to-head comparisons when prospective randomization is either unfeasible or (as in this case) potentially unethical.[12] Arguably, a more applicable analysis would have been one in which patients who received standard chemotherapy were excluded, thus creating a SCA more relatable to current standards. Including chemotherapy in the SCA skews the outcomes negatively, but probably not enough to explain the over 4-fold longer survival.

Other intriguing findings reported in the longer-term follow-up from ZUMA-3 have been correlatives pertaining to the kinetics of CAR-T expansion and persistence and their association with outcome. In one such study,[13] the median peak level and median area under the curve of CAR-T cell levels in blood between Days 0–28 ($AUC_{0–28}$) were approximately half as high in patients previously treated with blinatumomab compared to those not previously given this agent; these differences were not statistically significant, however ($p = 0.11$ and 0.16, respectively). On the contrary, both peak levels and $AUC_{0–28}$ were numerically similar when compared by prior inotuzumab ozogamicin exposure. Previous treatment with both blinatumomab and inotuzumab ozogamicin were associated with inferior OS, though not to a statistically significant degree. Overall, these data may point toward a mechanism of resistance induced by exposure to blinatumomab that could subsequently blunt the effects of brexu-cel. Alternatively, these non-significant differences may be due to chance alone from small subgroups, with the worse survival simply reflecting the challenge of treating heavily pretreated cases.

Another observation worth noting relates to an analysis of CAR-T persistence after treatment with brexu-cel. Among patients in the phase II portion from whom sufficient samples were available, 79% (22 of 28) had no detectable CAR-T cells at 6 months from brexu-cel infusion. What's more, 100% (10 of 10) of evaluable patients at 24 months (including ongoing responders) lacked detectable CAR-T cells. These data were part of the presentation at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting but not explicitly referenced in the published abstract.[14] While little can be deduced from small samples like this, these data suggest that long-term CAR-T persistence is neither expected nor necessary for favorable outcomes with brexu-cel. This has implications when considering the potential role of consolidation or maintenance therapies after response to brexu-cel: One of the main hypothetical drawbacks to such

intervention is the risk of inhibiting or ablating activity of persistent CAR-T cells. However, if there is no expectation that the cells are still present, then this concern is moot. This rationale seems to bear out in some additional studies that have come from post-approval experience with brexu-cel, which we will describe next.

Real-World Data of Brexu-Cel Use in R/R B-ALL

Following the FDA approval of brexu-cel in October 2021 based upon the results of the ZUMA-3 study, this agent became the primary CD19 CAR-T product used for adults with R/R B-ALL. Shortly thereafter, a consortium of US cancer centers was formed with the title Real-World Outcomes Collaborative of CAR-T in Adult ALL (ROCCA).[15–17] The purpose of this initiative was to investigate "real-world" outcomes of brexu-cel when used as an FDA-approved therapy (ie, off-study) in adults with R/R B-ALL. Participating centers curated deidentified patient data of adults who had received brexu-cel for R/R B-ALL off-study and submitted this to a centralized database, upon which data from all participating centers was compiled and analyzed. With the most recent data lock occurring on October 30, 2023, there were a total of 31 participating institutions. Eligible patients included adults ≥18 years-old treated with commercial brexu-cel for R/R B-ALL at a participating center: demographic and outcomes data including response rates, toxicity (including CRS and ICANS), and survival estimates, were obtained.

In the first publication from this effort, 189 patients were infused with brexu-cel: the median age was 46, with a median of 4 prior lines of therapy.[17] Among patients with available pre-leukapheresis disease assessment, 42% of patients were in morphologic remission: among these, 27% had detectable or unknown MRD status, while 15% were in MRD- CR. Median time from leukapheresis to infusion (aka "vein-to-vein" time, not product release as reported in ZUMA-3) was 33 days (IQR: 26–42 days).[18] Regarding bridging therapy, 65% (n = 123) received a variety of options, from which combinations were frequent: most common was chemotherapy (64%, n = 79), followed by forms of targeted immunotherapy (26%, n = 32), tyrosine kinase inhibitors (TKI; 19%, n = 23), and corticosteroids (12%, n = 15); intrathecal chemotherapy was added as a complementary treatment to 28 patients (23%).[17]

Of the 168 response-evaluable patients, 90% (n = 151) achieved a morphologic CR at Day +28 response assessment, 79% of which were MRD- (at a detection threshold of at least 10^{-4}, including MFC, RT-PCR, or next-generation sequencing [NGS] methodologies).[17] Among the responders, 30 (20%) received consolidative HCT, 18 (n = 12%) received TKI as post-CAR-T maintenance, and 11 (7%) received other forms of maintenance (mostly POMP chemotherapy). In all infused patients, from whom the median follow-up was 11.4 months, the median OS was not reached, and the median progression-free survival (PFS; first occurrence of disease progression or death) was 9.5 months. In univariate analyses for predictors of PFS, patients with Ph+ disease fared significantly better (HR 0.57, 95% CI: 0.35–0.97), but Ph-like disease did not (HR 0.80, 95% CI: 0.46–1.40); however, these were not observed in multivariable models. In fact, the only two factors associated with significantly better PFS in multivariable models from this cohort were having received HCT prior to brexu-cel (HR 0.41, 95% CI: 0.22–0.76, p = 0.004) and undergoing HCT after achieving remission with brexu-cel (HR 0.34, 95% CI: 0.14–0.85, p = 0.02).[17]

In a previous analysis, when the ROCCA cohort included 152 treated patients, 82% (n = 125) developed any-grade CRS and 10% (n = 13) developed grade 3+ CRS; 56% (n = 85) developed any-grade ICANS and 31% (n = 48) developed grade 3+ ICANS. The development of grade 3+ CRS was associated with a higher hazard of death (HR 2.38, 95% CI: 1.00–5.66, p = 0.05); there was also a numerically greater risk of relapse or death (EFS failure) in those experiencing grade 3+ CRS (HR 1.81, 95% CI, 0.87–3.79, p = 0.12). Similar trends were not seen in those experiencing grade 3+ ICANS.[19]

In comparing results of the ZUMA-3 trial with those of the ROCCA study (with the caveat of cross-study comparisons), several factors stand out (Figure 1). First, the demographics appear relatively comparable, in that the median age was in the 40s, with most patients heavily-pretreated, and >40% of patients having previously received HCT. Compared to the ZUMA-3 study – where patients needed >5% blasts to be eligible – a larger proportion of patients on the ROCCA study had their disease in remission at the time of leukapheresis. The median "vein-to-vein" time was slightly longer off-study, after accounting for the differences in how this metric was reported (ie, time to product release in ZUMA-3 vs time to infusion in ROCCA; the former of which does not include time to deliver lymphodepletion, etc). The response rates in the real-world setting appeared higher than those treated on the ZUMA-3 study (90% vs 71%

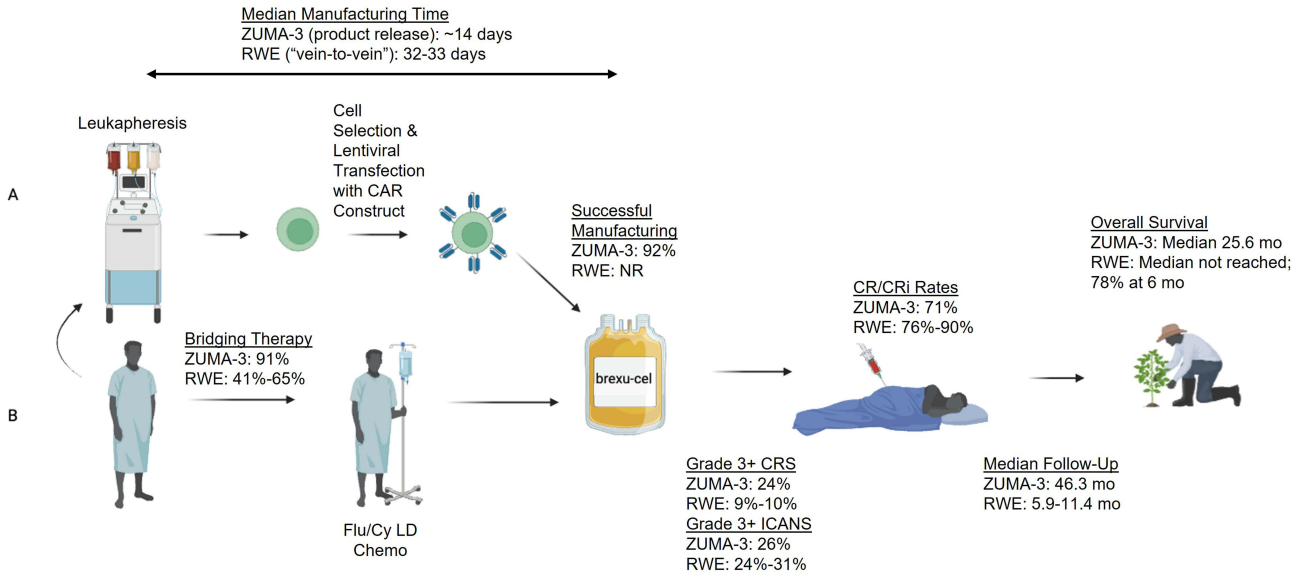

Figure 1 Overview of treatment with brexucabtagene autoleucel with summary of key data. Column (**A**) depicts the procedure of leukapheresis for brexu-cel production: brexu-cel undergoes an additional cell-selection step to remove leukemic blasts to avoid ex-vivo T-cell activation and exhaustion. Following this step, the cells are transfected with a vector containing a CD3-*zeta* and CD28 costimulatory domain. Patients are then treated with 1×10^6 viable chimeric antigen receptor-modified T (CAR-T) cells/kg. Column (**B**) depicts the clinical timeline for patients while they await production of their brexu-cel product: this often entails bridging therapy if needed, followed by lymphodepleting (LD) chemotherapy with fludarabine 25mg/m^2 IV on Days −4 through −2 and cyclophosphamide 900mg/m^2 IV on Days −2 (Flu/Cy). The overlaid writing includes results from endpoints of interest from the pivotal ZUMA-3 trial and from two real-world evidence (RWE) studies, which are described further in the text (see these studies[5,9,16–20]). Created in BioRender. Kopmar, N. (2024) https:// BioRender.com/x46b947.

Abbreviations: CR/CRi, complete remission or complete remission with incomplete hematology recovery; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; mo, months; NR, not reported.

among infused patients). While the higher initial response rates observed on the ROCCA study might be in-part related to more patients having low disease burden at leukapheresis than on ZUMA-3, there was ultimately no association between disease burden at leukapheresis and post-CAR-T PFS or OS in the ROCCA study.[17] Finally, the rates of grade 3+ ICANS were higher on the ROCCA study: the latter finding is of unclear cause and significance, although might relate to an evolution and harmonization of the approach that centers use to grade neurologic toxicity (thereby potentially identifying cases of ICANS more frequently than previously identified).

This highlights the importance of performing real-world studies, particularly with CAR-T agents, which have all gained initial approval based off single-arm, phase II studies. Real-world studies often include many patients who would not have been eligible for the original clinical trial due to strict entry criteria in the latter. For instance, in the ZUMA-3 study, anyone with overt CNS disease was excluded; on the ROCCA study, 28 of 152 treated patients (18%) had CNS-2 or CNS 3 disease (outcomes for this subgroup of interest are described below).[21] Multiple ongoing studies to examine specific clinical questions of brexu-cel in R/R B-ALL are ongoing. And as of August 2024, the ROCCA consortium now has 35 participating US centers.

Similar to the work from the ROCCA consortium, a group of investigators has also interrogated the Center for International Blood & Marrow Transplantation Research (CIBMTR) database for a real-world experience with brexu-cel. Since CAR-T is a cellular therapy analogous to HCT, CIBMTR also collects data on patients treated at participating centers who receive this treatment. In an abstract presented at the 2023 American Society of Hematology (ASH) Annual Meeting, outcomes from 197 such patients were described.[20] In sum, their findings were similar to those described by the ROCCA group (Figure 1). Bridging therapy was given to 41%, and the median "vein-to-vein" time was 32 days (IQR: 27–42 days). The overall CR/CRi rate by Day 100 was 76%. RFS at 6 months was 53% (95% CI: 42–62%), while OS at 6 months was 78% (95% CI: 69–84%). Among those who responded to brexu-cel, 31% proceed to HCT. Rates of grade 3+ CRS and ICANS were 9% and 24%, respectively.

Given how data are reported to CIBMTR, it is assumed that many (if not all) of the patients comprising the ROCCA experience are also captured in this work. However, CIBMTR is limited to the information collected on data collection forms. This could prevent the interrogation of specific details that can only be ascertained by returning to the primary medical records, which were available (following necessary local regulatory approvals) to the ROCCA investigators. Therefore, it is suspected

that analyses from ROCCA may provide more granularity, even if the total patient numbers are less than those available to CIBMTR. Such distinctions may become more apparent if these abstracts ultimately yield peer-reviewed publications.

Practical Considerations of Brexu-Cel Use in B-ALL

We do not use a standardized algorithm or pathway to determine when brexu-cel is offered to individual patients with R/R B-ALL. Instead, we rely on multiple factors, which have been summarized previously.[22] In general, disease control must be sufficient to allow for the multiple steps required before brexu-cel can actually be administered: not only leukapheresis and cell manufacturing but also the time needed for financial authorization (a particularly complex topic in the US with third-party payers, which is beyond the scope of this review but worthy of its own analysis). This issue alone often requires the administration of some other treatment, which (if sufficiently effective) obviates the need for CAR-T unless relapse occurs later. This is highlighted by the ROCCA data, in which a significant proportion of patients (42%) were in a CR at the time of leukapheresis.[17] Indeed, in such cases where the goal is to proceed to HCT once the patient gets back into remission, we may proceed directly to HCT if circumstances (eg, depth of remission, donor availability, etc.) permit. Second, because of the requirements for caregiver support and lodging within a short distance from our center, it must also be logistically feasible. In terms of criteria that are more medically based, comorbidities that could be prohibitively risky in the context of severe CRS or ICANS (eg, significant cardiovascular disease, chronic kidney disease) represent relative contraindications. These issues often require input from subspecialists for risk stratification, analogous to perioperative evaluations. While the role of consolidative HCT after response to brexu-cel remains somewhat controversial, we may favor brexu-cel in those unlikely to be candidates for HCT, since it appears that long-term remission with this as a stand-alone therapy is possible.[9]

A key reason we do not use a standardized approach is the complexity that goes into the optimal sequencing of the different immunotherapy strategies available. There are no convincing data to suggest that the use of inotuzumab ozogamicin or blinatumomab substantially alters subsequent CAR-T efficacy.[13,23] As mentioned above, analyses that suggest inferior outcomes for patients previously treated with these agents may simply reflect the tendency of all malignancies to become increasingly resistant as lines of therapy increases. Furthermore, there is an inherent selection bias in retrospective studies such as these that unavoidably exclude patients who had the best outcomes with these earlier treatment approaches. In other words, the subset of patients who experience long-term remission following a response to inotuzumab ozogamicin or blinatumomab (whether consolidative HCT is used or not) will not require any further systemic therapy. Such patients will never be included in these comparisons of response to CAR-T. As such, only those who experience relative failure of these respective agents when previously exposed are counted. For this reason, one cannot take these fundamentally biased analyses as evidence that CAR-T should be offered earlier. This is particularly true if circumstances suggest that blinatumomab or inotuzumab ozogamicin may be a better option at that particular time.

Once the decision is made to pursue brexu-cel, the issue of bridging therapy often arises. Again, due to the complexity of these cases, we do not adhere to a specific approach for all patients. The primary goal is to achieve sufficient disease control to traverse the time needed for cell manufacturing, infusion, and (not to be forgotten) post-infusion expansion and anti-leukemia activity. Considering the "vein-to-vein" data reported above, this could span approximately 5 weeks. On the other hand, excess toxicity must be avoided, as this could jeopardize the patient's candidacy to proceed with brexu-cel once it is available. Indeed, this specifically was the most common reason that patients on ZUMA-3 who enrolled (ie, underwent leukapheresis) were not able to proceed.[5] When considering these factors, a frequent approach used at our center is to administer 1 or 2 individual doses of inotuzumab ozogamicin. This was not an option for patients treated on ZUMA-3, but its high response rates (particularly in states of high disease burden) and relatively good short-term safety profile following brief exposure make it appealing in this situation.[18,24] Alternatively, we might use non-myelosuppressive agents like vincristine with or without dexamethasone, particularly if intervention is needed to control rapidly-progressive disease identified just prior to starting lymphodepletion. Patients with concurrent or recent CNS disease require additional consideration, and this topic is addressed below.

Adults aged 18–25 are technically eligible for both brexu-cel and tisa-cel, posing another difficult question: which CAR-T product should be used. There has been no prospective comparison between these two respective agents, and the decision regarding the optimal CAR-T product for such patients needs to be individualized. Retrospective data comparing real-world outcomes in this age cohort[25] suggest similar response rates between the two respective products, but does indicate increased toxicity with brexu-cel (ie, higher rates of grade 3+ CRS and

ICANS): individual patient factors including pre-existing comorbidities and pre-CAR-T disease burden need to be considered when facing this product choice in the AYA population.

Ultimately, most patients treated with brexu-cel for R/R B-ALL at our center not previously subjected to HCT will be referred for consolidative HCT following brexu-cel. We acknowledge that the role of HCT following CD19 CAR-T for B-ALL remains somewhat controversial, with practices varying across different institutions. Part of the controversy is that no prospective studies designed to specifically interrogate this question have been completed, and the data that do exist are confounded by heterogeneity with respect to CAR-T construct (4-1BB vs CD28) and age group (pediatrics/AYA vs adults) across trials. Only a small minority of patients enrolled in the ELIANA study had subsequent HCT, and there was no difference in EFS or OS observed.[3] However, several studies (including both CD28- and 4-1BB-based constructs, the former in pediatrics and the latter in adults) support the EFS benefit of consolidative HCT following CAR-T.[26,27] More recently and discussed previously, the ROCCA study has presented real-world data that further support the use of consolidative HCT following brexu-cel.[16,17] Additionally, other consolidative therapies, such as TKI therapy in the case of Ph+ disease, were shown to improve PFS in a landmark analysis in the first presentation of the ROCCA data.[16] In the case of Ph+ patients, we typically will recommend TKI maintenance, regardless of whether they receive consolidative HCT post-CAR-T. The optimal duration of post-CAR-T and post-HCT TKI maintenance is not well-established. That said, offering TKI for a minimum of 1 year would be a reasonable goal for most cases until better evidence is available.[28]

Emerging evidence supports the notion that the use of NGS-based MRD detection techniques (eg, ClonoSEQ, capable of detecting MRD at the level of 10^{-6}) will better allow us to discern which patients with B-ALL are more likely to sustain durable remissions post-CAR-T and potentially forego consolidative HCT.[17,29] Inspired in part by findings like these, an interventional trial is currently enrolling in the pediatric/AYA setting, in which consolidative transplant is deferred in patients achieving MRD- by NGS at Day 28 (NCT05621291); to date, no such trial is open to accrual in adult patients receiving brexu-cel. Only a well-designed prospective trial will be able to demonstrate if this strategy is feasible given the time needed to obtain results from MRD testing, coordinate with the transplant center, etc. Further, only a randomized trial where this approach is compared to one where salvage therapy is offered at the first sign of clinically-apparent relapse would be able to say definitively which strategy is superior; such a trial would be incredibly complex and thus seems aspirational in the near-term.

Certain unique considerations about brexu-cel bear discussion. First is its use in patients with overt CNS disease (CNS-2 or CNS-3): recall that such patients were excluded from ZUMA-3. Recent retrospective data from the ROCCA collaborative have described very high CNS response rates with brexu-cel (close to 90% CNS disease clearance) with no significant increase in toxicity as compared to CNS-negative counterparts;[21] the main confounder is that many patients included on this study with active CNS disease at pre-CAR-T staging received CNS-directed bridging therapy and did not undergo repeat staging prior to brexu-cel infusion. We prefer the use of brexu-cel over inotuzumab ozogamicin (which does not cross the blood-brain-barrier and no evidence exists to support its isolated use for this purpose) or blinatumomab (data regarding CNS activity is limited to 1 retrospective case series) in the case of R/R B-ALL with active CNS disease.[30] Patients typically receive bridging with intrathecal chemotherapy with or without CNS-active systemic chemotherapy, and in rare instances radiotherapy. Longer-term follow-up will be required to determine whether the apparent CNS activity of brexu-cel – as manifest in these high CNS response rates – translates into durable CNS remissions.

Future Directions of CAR-T in R/R B-ALL

With the results of the E1910 study and recently-expanded approval of blinatumomab as consolidation for Ph- B-ALL,[31] as well as the increasing interest in the use of this agent as part of frontline therapy for Ph+ B-ALL,[32–34] it is conceivable that most adults with B-ALL in high-resource areas will receive blinatumomab as part of their initial treatment. If this occurs, it could introduce new challenges in the delivery of brexu-cel and other CD19 CAR-T products in the R/R setting. For example, this change in practice may yield fewer relapses overall, which of course is a positive development. However, as referenced above, prior exposure to blinatumomab may impact the activity of CD19 CAR-T cells.[13] If these relapses now possess greater resistance to other forms of CD19-directed immunotherapy (eg, antigen loss or modification, other mechanisms that counteract immune-mediated cytotoxicity), it could reduce the probability of successful results with these CAR-T products. Based on the available evidence, if CD19 is still expressed, we believe it is still appropriate to offer brexu-cel or other CD19 CAR-T products to patients

who relapse despite receiving blinatumomab during their frontline therapy. Ultimately, time and experience with this specific scenario will tell us if this remains an effective strategy.

Since the FDA approval of brexu-cel in October 2021, this has been the only commercially-available CAR-T product for the majority of adults with R/R B-ALL (excluding the AYA subset <26 years-old, who are also eligible for tisa-cel). However, a new CD19 CAR-T product – obecabtagene autoleucel (obe-cel; AUTO1) – is (as of this writing) poised to be a new addition to the armamentarium against R/R B-ALL. Obe-cel is a unique CD19 CAR-T product, designed to have "fast-off" CD19 binding kinetics,[35] thought to prevent early T-cell exhaustion as well as CAR-T-mediated immunologic toxicity. Obe-cel was studied in R/R B-ALL in the open-label, multicenter, phase Ib/II FELIX study.[36–38] Following lymphodepleting chemotherapy with flu/cy, obe-cel was given in split-dosing on Days 1 and Day 10: the target dose was 410×10^6 CAR-T cells, based upon the pre-lymphodepletion bone marrow disease burden. One hundred fifty-three patients were enrolled, and 127 enrolled patients were ultimately infused with obe-cel. The median age of trial enrollees was 47 years-old, with 44% having received prior HCT, 42% prior blinatumomab, and 31% prior inotuzumab ozogamicin. With a median follow-up of 16.6 months, the overall CR/CRi rate was 78%, 97% of which were MRD- by MFC. Among responders (n=99), 17% proceeded to consolidative HCT. The 12-month EFS rate was 50%, and the 12-month OS rate was 61%.

Beyond response rates and survival outcomes, the results from the FELIX trial provide evidence of two potential benefits of obe-cel as compared to brexu-cel. First, the very low rates of any grade 3+ CRS (<3%) or ICANS (<8%) seen with obe-cel, well below the rates of CRS and ICANS seen with brexu-cel in either the ZUMA-3 study[5] or with real-world outcomes on the ROCCA and CIBMTR studies.[19,20] Second, CAR-T persistence was seen in the majority of responders with obe-cel. Patients who lost CAR-T persistence or B-cell aplasia following obe-cel had a 2.9 or 1.7 fold risk of relapse or death, respectively.[38] Alternatively, and as noted above, the vast majority of patients treated on the ZUMA-3 study lost CAR-T persistence at 6 months, including a subset of ongoing long-term responders.[14] Multiple studies suggest that loss of CAR-T persistence (either via direct measurement or indirectly via monitoring of B-cell aplasia) corresponds with a higher risk of disease recurrence and death.[29,39,40] One counterpoint to this body of evidence is the concept of immortal time bias:[41] in order to experience long-term CAR-T persistence, one must not relapse and/or die early. This creates an association between better outcomes and CAR-T persistence when such an association does not truly exist. Ultimately, longer follow-up will be required to fully assess the degree of ongoing CAR-T persistence, and its implications for relapse/survival, on the FELIX study.

These factors – favorable toxicity profile and enhanced in vivo CAR-T persistence – are promising. However, longer follow-up from the FELIX study is required. The data also must undergo rigorous evaluation by a peer-reviewed journal (as of this writing, these data have only been presented in abstract form) as well as the FDA. Additionally, real-world studies of obe-cel use following its anticipated approval will be helpful to fully inform a decision about whether to offer a patient with R/R B-ALL brexu-cel or obe-cel.

Conclusion

Brexu-cel has been a breakthrough for adults with R/R B-ALL and has led to high response rates and durable responses with or without HCT and/or other consolidative therapy. Real-world data indicate that a high percentage of adult patients respond to brexu-cel, although rates of grade 3+ ICANS may be slightly higher than in the study setting. More knowledge is critically needed about the pathophysiology and potential treatment options for severe ICANS, particularly when considering the use of this product in R/R B-ALL. Ongoing studies under the ROCCA collaborative include investigations into toxicities, CNS disease, and a comparison between brexu-cel and tisa-cel in AYA patients. Other issues that have yet to be optimized with brexu-cel include the ideal sequencing strategy with respect to other immunotherapies available for R/R B-ALL and the best approach to bridging therapy. In the future, similar collaborative efforts to assess the real-world outcomes of obe-cel in R/R B-ALL will be of benefit, and a comparison between real-world outcomes of brexu-cel vs obe-cel will be useful to help inform the optimal use of each respective agent in R/R B-ALL moving forward (given that a head-to-head prospective comparison will be unlikely in the foreseeable future).

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Author Contributions

NEK and RDC conceived of, drafted and approved the final version of the manuscript; NEK and RDC made the figure All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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