15 September 2022
EMA/804955/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Yescarta

International non-proprietary name: axicabtagene ciloleucel

Procedure No. EMEA/H/C/004480/II/0046

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| ABC | activated B cell |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{0-28}$ | area under the curve from Treatment day 0 to 28 |
| auto-SCT | autologous stem cell transplant |
| BSA | body surface area |
| CAR | chimeric antigen receptor |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | confidence interval |
| CNS | central nervous system |
| CORAL | Collaborative Trial in Relapsed Aggressive Lymphoma |
| CR | complete response |
| CRP | C-reactive protein |
| CRS | cytokine release syndrome |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CXCL | C-X-C motif chemokine |
| DLBCL | diffuse large B-cell lymphoma |
| DOR | duration of response |
| $EBV^+$ | Epstein-Barr virus-positive |
| ECOG | Eastern Cooperative Oncology Group |
| EFS | event-free survival |
| ELISA | enzyme-linked immunosorbent assay |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 |
| EQ-5D-5L | Euro-QoL, 5 Dimensions, 5 Levels |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FL | follicular lymphoma |
| GCB | germinal center B cell |
| GM-CSF | granulocyte-macrophage colony-stimulating factor |
| GVHD | graft-versus-host disease |
| HDT | high-dose therapy |
| HGBL | high-grade B-cell lymphoma |
| HR | hazard ratio |
| ICAM-1 | intercellular adhesion molecule-1 |
| IFN | interferon |

| | |
|---|---|
| IL | interleukin |
| IxRS | Interactive Voice/Web (x) Response System |
| KM | Kaplan-Meier |
| LBCL | large B-cell lymphoma |
| LLOQ | lower limit of quantification |
| MCP-1 | monocyte chemotactic protein |
| MDC | macrophage-derived chemokine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mEFS | modified event-free survival |
| MIP | macrophage inflammatory protein |
| MST | MedDRA search terms |
| NCI | National Cancer Institute |
| NHL | non-Hodgkin lymphoma |
| NOS | not otherwise specified |
| ORR | objective response rate |
| ORCHARRD | Ofatumumab Versus Ritixumab Salvage Chemoimmunotherapy in R/R DLBCL |
| OS | overall survival |
| PBMC | peripheral blood mononuclear cell |
| PD | progressive disease |
| PFS | progression-free survival |
| PMBCL | primary mediastinal B-cell lymphoma |
| PML | progressive multifocal leukoencephalopathy |
| PR | partial response |
| PRO | patient-reported outcome |
| PT | preferred term |
| QoL | quality of life |
| R-CHOP | rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone |
| RCR | replication-competent retrovirus |
| R-EPOCH | rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisolone |
| r/r | relapsed/refractory |
| SAA | serum amyloid A |
| SAE | serious adverse event |
| sAAIPI | second-line age-adjusted International Prognostic Index |
| SD | stable disease |
| SOCT | standard of care therapy |
| TEAE | treatment-emergent adverse event |
| $T_{eff}$ | effector T-cell phenotype |
| $T_{em}$ | effector memory T-cell phenotype |
| $T_{naïve}$ | naïve T-cell phenotype |
| US | United States |
| VAS | visual analog scale |

| | |
|---|---|
| VCAM-1 | vascular cell adhesion molecule-1 |
| VEGF | vascular endothelial growth factor |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Kite Pharma EU B.V. submitted to the European Medicines Agency on 5 November 2021 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of indication to include treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) for Yescarta; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the product information with minor editorial changes.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

## *Information relating to orphan designation*

Yescarta, was designated as an orphan medicinal product EU/3/14/1393 on 2014-12-16. Yescarta was designated as an orphan medicinal product in the following indication: Treatment of diffuse large B cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Yescarta as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004480/human_med_002292.jsp

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0132/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0132/2020 was not yet completed as some measures were deferred.

### *Information relating to orphan market exclusivity*

#### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

### *MAH request for additional market protection*

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

### *Protocol assistance*

The MAH received Protocol Assistance from the CHMP on 3 September 2017 (EMEA/H/SA/3117/5/2017/PA/SME/ADT/PR/II). The Protocol Assistance pertained to clinical aspects of the dossier.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CAT were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Claire Beuneu

| Timetable | Actual dates |
|---|---|
| Submission date | 5 November 2021 |
| Start of procedure: | 27 November 2021 |
| CAT Rapporteur Assessment Report | 25 January 2022 |
| CAT Co-Rapporteur Assessment Report | 31 January 2022 |
| PRAC Rapporteur Assessment Report | 28 January 2022 |
| PRAC members comments | 2 February 2022 |
| CAT and CHMP members comments | 8 February 2022 |
| PRAC Outcome | 10 February 2022 |
| Updated CAT Rapporteur(s) (Joint) Assessment Report | 14 February 2022 |
| CAT Request for Supplementary Information (RSI) | 18 February 2022 |
| CAT Rapporteur Assessment Report | 14 April 2022 |
| PRAC Rapporteur Assessment Report | 21 April 2022 |
| PRAC members comments | 26 April 2022 |
| Updated PRAC Rapporteur Assessment Report | 28 April 2022 |
| CAT and CHMP members comments | 3 May 2022 |
| PRAC Outcome | 5 May 2022 |
| Updated CAT Rapporteur Assessment Report | 6 May 2022 |

| Timetable | Actual dates |
|---|---|
| CAT Request for Supplementary Information (RSI) | 13 May 2022 |
| PRAC Rapporteur Assessment Report | 23 June 2022 |
| PRAC members comments | n/a |
| CAT Rapporteur Assessment Report | 30 June 2022 |
| CAT and CHMP members comments | 6 July 2022 |
| PRAC Outcome | 7 July 2022 |
| Updated CAT Rapporteur Assessment Report | 13 July 2022 |
| CAT Request for Supplementary Information (RSI) | 15 July 2022 |
| PRAC members comments | 23 August 2022 |
| CAT Rapporteur Assessment Report | 17 August 2022 |
| CAT and CHMP members comments | 31 August 2022 |
| PRAC Outcome | 1 September 2022 |
| CAT Opinion | 9 September 2022 |
| CHMP Opinion | 15 September 2022 |
| The CHMP adopted a report on similarity of Yescarta with Kymriah, Minjuvi, Polivy on 15 September 2022 | 15 September 2022 |

# 2. Scientific discussion

## *2.1. Introduction*

### *2.1.1. Problem statement*

#### *Disease or condition*

Large B-cell lymphoma (LBCL) represents a subset of aggressive B-cell non-Hodgkin lymphoma (NHL) and includes both diffuse large B-cell lymphoma (DLBCL) (including DLBCL not otherwise specified [NOS]) and high-grade B-cell lymphoma (HGBL).

#### *State the claimed the therapeutic indication*

Axicabtagene ciloleucel is proposed for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B cell lymphoma (HGBL).

Following the first round of responses to the RfSI, the MAH modified the intended indication as follows:

Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) who are refractory or have relapsed within 12 months from completion of first-line therapy.

## *Epidemiology and risk factors, screening tools/prevention*

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B lymphocytes and, to a lesser extent, in T lymphocytes and natural killer cells. NHL is the most prevalent hematological malignancy and is the seventh most common new cancer, accounting for 4% of all new cancer cases and 3% of cancer related deaths in the US. In Europe, NHL is the 12th most common new cancer, accounting for 3% of all new cancer cases and 3% of cancer related deaths.

LBCL is an aggressive subset of B-cell NHL, representing 30% to 40% of NHL cases. The most common LBCL subtype is DLBCL (including DLBCL not otherwise specified [NOS]), which accounts for more than 80% of LBCL cases. In 2016, the World Health Organization (WHO) introduced HGBL as a new category of LBCL. HGBL represents up to 13% of LBCL cases.

## *Clinical presentation, diagnosis and stage/prognosis*

LBCL subtypes include DLBCL NOS (defined by exclusion of unique features and further divided according to cell of origin types, germinal center B cell [GCB] and activated B cell [ABC]), and other disparate DLBCL entities with unique clinical and pathological features such as primary DLBCL of the central nervous system (CNS); primary cutaneous DLBCL, leg type; Epstein Barr virus positive (EBV+) DLBCL NOS; EBV+ mucocutaneous ulcer; DLBCL associated with chronic inflammation; and T cell/histiocyte-rich LBCL. LBCL also includes DLBCL arising from follicular lymphoma (FL), but this subtype is not included in the WHO 2016 categorization due to the classification being based on the investigator's assessment of the clinical history of FL and not solely on histopathology. HGBL comprises 2 subcategories: 1) HGBL with MYC, BCL2, and/or BCL6 rearrangements, which is also known as double- or triple-hit lymphoma and excludes FL or lymphoblastic lymphoma; and 2) HGBL NOS, which includes LBCL that are "high-grade" and would be previously characterized as B cell lymphoma unclassifiable, and lack genetic features of double- or triple hit lymphomas.

## *Management*

The current standard of care for the first-line treatment of DLBCL is the chemotherapeutic regimen cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in combination with the anti-CD20 monoclonal antibody rituximab (R-CHOP). Treatment with this regimen resulted in 5-year and 10-year event-free survival (EFS) rates of 47% and 35%, respectively, and 5-year and 10-year overall survival (OS) rates of 58% and 44%, respectively in patients 60 to 80 years of age. For patients 18 to 60 years of age treated with R-CHOP, 3-year EFS and OS rates are 79% and 93%, respectively. While R-CHOP has improved outcomes for patients with DLBCL overall, about 10% to 15% of patients have primary refractory disease and a further 20% to 40% of patients have disease that relapses.

The optimal therapy for the first-line treatment of patients with HGBL has not been established. A dismal prognosis has been reported for patients with HGBL treated with various chemoimmunotherapy regimens, and there is no consensus whether regimens more intensive than R-CHOP are required. Retrospective data with more intensive regimens such as dose-adjusted rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisolone (DA-EPOCH-R) have shown benefit, and have also been reported as first-line treatment for HGBL. A recent retrospective analysis suggests rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisolone (R-EPOCH) may not improve survival outcomes compared with R-CHOP (4-year OS rates of 49.6% and 54.5%, respectively).

Standard second-line therapy in the curative setting for LBCL is comprised of rituximab and platinum-containing salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplant (auto-SCT) for those who are eligible. Five-year EFS rates of 46% and OS rates of 53% in patients with r/r NHL have been reported for subjects who received the definitive treatment (salvage chemotherapy and HDT-auto-SCT). The efficacy of this regimen has not been fully assessed for HGBL due to conflicting data from several studies.

While HDT-auto-SCT has curative potential, only half of patients respond to second-line salvage chemotherapy and are able to proceed to auto-SCT. Other reasons for not undergoing HDT-auto-SCT include failure to mobilize $CD34^+$ stem cells for auto-SCT, poor performance status, organ dysfunction, comorbidities, unresolved treatment-emergent toxicities, or age (HDT-auto-SCT is typically only recommended for patients younger than 60 to 70 years of age, depending on regional guidelines). Furthermore, disease progression can occur at any point preparing for or after auto-SCT and an increased risk of death is associated with auto-SCT due to early transplant-related mortality. Secondary malignancies, including treatment-related myelodysplastic syndrome and treatment-related acute myeloid leukemia, are also associated with HDT-auto-SCT.

Outcomes are particularly poor for patients who have primary refractory disease or early relapse after first-line therapies; further, most of these patients are not eligible for transplant due to their chemotherapy-resistant disease. Published objective response rates (ORRs) to second-line chemotherapy in patients with refractory or early relapse disease range from 14% to 55%. For patients who do not respond to salvage chemotherapy, a median OS of 4.4 months has been reported in one study.

Outcomes are also poor for patients with higher second-line age-adjusted International Prognostic Index (sAAIPI) scores. Studies have reported significantly higher 3-year EFS for patients with an sAAIPI of 0 or 1 factors compared with those who had 2 or 3 factors (40% versus 18%, respectively), and significantly improved OS and progression-free survival (PFS). A retrospective study demonstrated 4-year PFS rates for patients with low risk (0 factors), intermediate risk (1 factor), and high-risk (2 or 3 factors) sAAIPI of 70%, 39%, and 16%, respectively, and 4-year OS rates of 74%, 49%, and 18%, respectively.

More recently, 2 therapies were conditionally approved in the EU for treating transplant-ineligible patients with r/r DLBCL, and although these new treatment options offer incremental improvements in response rates for selective patients, neither therapy has demonstrated curative outcome. These therapies are tafasitamab, an anti-CD19 antibody, in combination with lenalidomide, with conditional approval based on results from a Phase 2 study and polatuzumab vedotin, an antibody-drug conjugate comprising a monoclonal antibody against CD79b conjugated to monomethyl auristatin E, in combination with bendamustine and rituximab, with conditional approval based on results from a Phase 1b/2 study.

In summary, many patients do not benefit from current standard of care second-line therapy. Although higher risk is associated with disease that is refractory or relapses within 12 months of first-line therapy, only 10% of all patients with r/r LBCL are estimated to have long-term survival following auto-SCT in the rituximab era. Thus, a need remains for alternative second-line therapies, including those with a mechanism of action independent of chemotherapy sensitivity.

### 2.1.1. About the product

Axicabtagene ciloleucel is an anti-CD19 chimeric antigen receptor (CAR) T-cell product manufactured from a patient's own T cells that are obtained by leukapheresis and transduced with a murine γ retroviral

vector to deliver an anti-CD19 CAR transgene, resulting in expression of the anti-CD19 CAR protein on the surface of the patient's engineered T cells. These engineered T cells are then introduced back into the patient via a single intravenous infusion and target the B cell marker, CD19.

The anti-CD19 CAR consists of a murine single-chain antibody fragment that specifically binds human CD19; the partial extracellular domain (hinge) and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte costimulatory receptor that plays an important role in optimizing T-cell survival and function; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor complex. After engagement of the anti-CD19 CAR with CD19+ target cells, the CAR intracellular domains trigger a dual signaling cascade that leads to CAR T-cell activation, proliferation, and secretion of cytokines, chemokines, and other molecules that recruit and activate additional antitumor immune cells and results in tumor cell lysis.

Axicabtagene ciloleucel has demonstrated the capacity to prolong survival as a third-line treatment for heavily pretreated patients whose disease was refractory to second-line therapy, and may present a favorable efficacy and tolerability profile as a second-line therapy. Since patients with r/r LBCL who are refractory to or relapse early after first-line chemotherapy may also be resistant to second-line or beyond chemotherapy, they may benefit from receiving therapies such as CAR T-cell therapy that have different mechanisms of action earlier in their treatment. Thus, administration of axicabtagene ciloleucel as a second-line therapy may result in further improvement in its efficacy and tolerability profile in patients with disease that failed first-line therapy, and particularly for patients with prognostic factors indicating they might respond poorly to second-line standard of care therapy (SOCT).

### 2.1.2. The development programme/compliance with CHMP guidance/scientific advice

In the EU, in accordance with Article 3(1) – Indent 1a – Advanced therapy medicinal product as defined in Article 2 of Regulation (EC) No 1394/2007, axicabtagene ciloleucel falls within the mandatory scope of the centralized procedure. Eligibility to the centralized procedure was confirmed by the Committee for Medicinal Products for Human Use (CHMP) on 26 May 2016 and axicabtagene ciloleucel was assigned the product reference H0004480.

Protocol assisstance for axicabtagene ciloleucel has been sought from the CHMP on 4 occasions, which are listed below. In general, CHMP advice has been followed throughout the development program.

- July 2015, focusing on the nonclinical development program and clinical study design of ZUMA-1 (Procedure number: European Medicines Agency [EMEA]/H/SA/3117/2/2015/ SME/ADT/III)
- December 2015, focusing on quality and the nonclinical development program (Procedure number: EMEA/H/SA/3117/3/2015/PA/SME/ADT/III)
- February 2017, focusing on quality and the nonclinical development program (Procedure number: EMEA/H/SA/3117/3/FU/1/2017/PA/SME/ADT/PR/II)
- September 2017, focusing on the clinical study design of study KTE-C19-107 (investigating DLBCL) (Procedure number: EMEA/H/SA/3117/5/2017 /PA/SME/ADT/PR/II)

### 2.1.3. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

## *2.2. Quality aspects*

No changes have been proposed as part of this extension of indication for manufacturing of the medicinal product. The product specifications remain the same.

## *2.3. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CAT. The environmental risk of axicabtagene ciloleucel is not affected by the proposed extension of indication.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| | | | | | |
|---|---|---|---|---|---|
| KTE-C19-107 (ZUMA-7) | 3 | Randomized, open-label; efficacy and safety; multicenter | Relapsed or refractory LBCL after first-line rituximab and anthracycline-based chemotherapy (adults) | Axicabtagene ciloleucel versus standard of care therapy | Enrollment complete<br>Study ongoing |

### 2.4.2. Pharmacokinetics

The pharmacokinetics (levels of anti-CD19 CAR T cells), pharmacodynamics (levels of serum analytes), other biomarkers, and product characteristics of axicabtagene ciloleucel were included as exploratory endpoints of ZUMA-7.

Methods

Subject samples were collected on the protocol-specified study visits (ie, Treatment days 0, 1, 3, and 7, with days relative to the infusion of axicabtagene ciloleucel on Treatment day 0; and on Study Days 50, 100, and 150 postrandomization, with days relative to the day of randomization on Study Day 0). Results were mapped to assessment time points that more accurately characterize pharmacokinetic and pharmacodynamic profiles and associations with clinical outcomes after treatment rather than

after randomization to the study (ie, Treatment days 0, 1, 3, and 7, Weeks 2 and 4, and Months 3, 6, 9, 12, 18, and 24 post-treatment).

The pharmacokinetic profile of axicabtagene ciloleucel in blood was assessed by means of measuring the presence, expansion, and persistence of anti-CD19 CAR T cells at multiple time points after cell infusion. Serial blood samples were taken after cell infusion and subjected to a validated quantitative polymerase chain reaction (qPCR) assay for the measurement of levels of anti-CD19 CAR T cells. The qPCR assay was based on the method developed by Kochenderfer and colleagues {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a} and was further optimized and validated by the University of Rochester Medical Center, Central Laboratory Services (University of Rochester Medical Center, Central Lab Services).

The maximum observed number of anti-CD19 CAR T cells/µg (ie, peak anti-CD19 CAR T cells/µL), the area-under-the-curve (AUC) of the level of anti-CD19 CAR T cells from infusion to Week 4 postinfusion ($AUC_{0-28}$), time-to-peak for anti-CD19 CAR T cells, and the persistence of anti-CD19 CAR T cells over time in blood were determined for subjects with evaluable samples. Due to the timing of samples collected after infusion, the calculated values for peak, $AUC_{0-28}$, and time-to-peak are considered estimates. The lower limit of detection (the sensitivity of quantitative detection of CAR T-cell signal above background at a level of precision acceptable for quantitation) was established at 1 anti-CD19 CAR T cell equivalent per 100,000 peripheral blood mononuclear cells (PBMCs), and the lower limit of quantification (LLOQ) was established at 8 to 110 cell equivalents per 100,000 PBMCs depending on DNA sample load.

Analyses of the pharmacokinetics assessments were performed on samples from subjects randomized to receive axicabtagene ciloleucel and who received at least 1 dose of axicabtagene ciloleucel (safety analysis set).

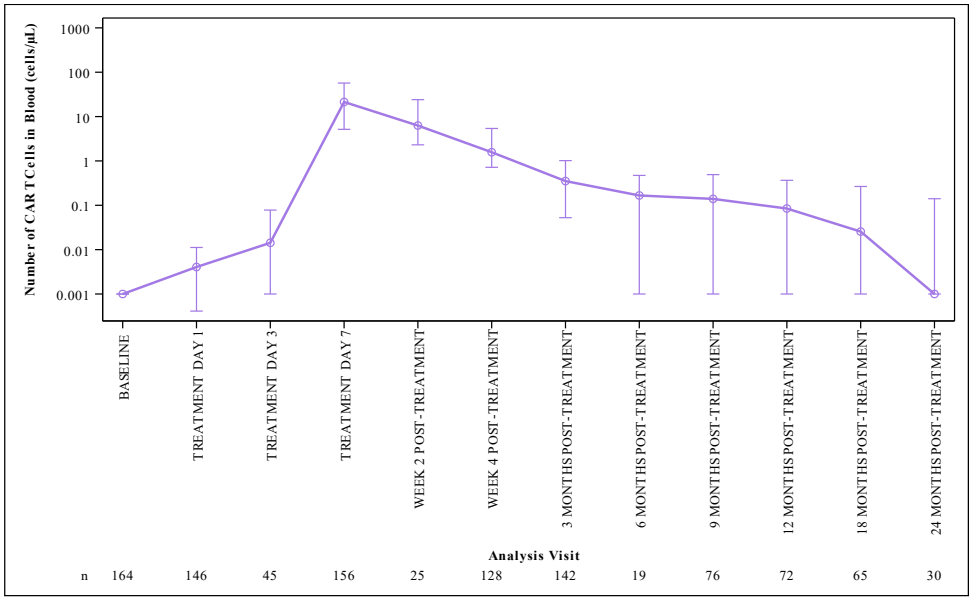
## *Pharmacokinetics results*

Anti-CD19 CAR T-cell levels in blood

Anti-CD19 CAR T cells were measurable in the peripheral blood of 162 evaluable subjects within the first 28 days after axicabtagene ciloleucel infusion. The median peak anti-CD19 CAR T-cell level was 25.84 cells/µL (range: 0.04 to 1173.25 cells/µL) and median $AUC_{0-28}$ was 236.23 cells/µL•days (range: 0.00 to $1.65 \times 10^4$ cells/µL•days). The median time-to-peak was calculated as 8 days (range: 2 to 233 days) (ie, 7 days after the day of axicabtagene ciloleucel infusion). By Month 3, median levels of anti-CD19 CAR T cells decreased towards baseline in evaluable subjects (0.35 cells/µL; range: 0.00 to 28.44 cells/µL) but were still detectable in 12 out of 30 evaluable subjects until 24 months post treatment.

A median line plot showing median anti-CD19 CAR T-cell levels over time is presented in the following Figure.

**Figure 1. Median Number (Q1, Q3) of Anti-CD19 CAR T Cells in Blood Over Time (Safety Analysis Set)**

1. 


Data cutoff date = 18MAR2021.
Abbreviations: CAR, chimeric antigen receptor; Q, quartile.
Note. Only subjects in axicabtagene ciloleucel arm are included.

One subject had a time-to-peak of anti-CD19 CAR T-cell level 233 days after the axicabtagene ciloleucel infusion. The late peak calculated for this subject was due to there being no sample available between Day 1 and Month 3. The value of CAR T cells/µL of blood at 233 days for this subject was low (< 1 cell/µL) and consistent with the overall pharmacokinetic profile across the study.

## *Special populations*

ZUMA-7 was not designed to test for differences between subgroups and formal comparisons were not prespecified. The statistical results of the subgroup analyses are considered descriptive only. Subjects in which peak anti-CD19 CAR T-cell levels and $AUC_{0\text{-}28}$ could not be derived were excluded from the respective summary statistics.

*Age*

Per protocol, all subjects were age ≥ 18 years. A total of 121 subjects were < 65 years of age and 49 subjects were ≥ 65 years of age.

Median peak anti-CD19 CAR T-cell level was 23.45 cells/µL (range: 0.09 to 622.50 cells/µL) in subjects < 65 years of age and 34.80 cells/µL (range: 0.04 to 1173.25 cells/µL) in subjects ≥ 65 years of age. The median $AUC_{0\text{-}28}$ was 218.84 cells/µL•days (range: 0.00 to 8541.63 cells/µL•days) in subjects < 65 years of age and 445.11 cells/µL•days (range: 0.00 to $1.65 \times 10^4$ cells/µL•days) in subjects ≥ 65 years of age. The median time-to-peak was 8 days for both subjects < 65 and ≥ 65 years of age.

*Sex*

A total of 106 subjects were male and 64 subjects were female.

The median peak anti-CD19 CAR T-cell levels were 25.84 cells/µL (range: 0.04 to 622.50 cells/µL) in female subjects and 25.70 cells/µL (range: 0.30 to 1173.25 cells/µL) in male subjects. The median $AUC_{0-28}$ was 243.60 cells/µL•days (range: 0.00 to 8541.63 cells/µL•days) in female subjects and 236.23 cells/µL•days (range: $4.02 \times 10^{-3}$ to $1.65 \times 10^{4}$ cells/µL•days) in male subjects. The median time-to-peak was 8 days for both female and male subjects.

*Race*

A total of 138 subjects were White, 11 subjects were Asian, 9 subjects were Black or African American, and 12 subjects self-reported their race as other (Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, and "other" according to the electronic case report form).

Median peak anti-CD19 CAR T-cell levels were 83.11 cells/µL (range: 8.41 to 622.50 cells/µL) in Asian subjects, 53.04 cells/µL (range: 0.41 to 276.28 cells/µL) in subjects self-reporting as other, 40.39 cells/µL (range: 0.55 to 198.99 cells/µL) in Black or African American subjects, and 22.68 cells/µL (range: 0.04 to 1173.25 cells/µL) in White subjects. The median $AUC_{0-28}$ was 1059.21 cells/µL (range: 67.01 to 8541.63 cells/µL•days) in Asian subjects, 586.03 cells/µL•days (range: 5.30 to 3759.66 cells/µL•days) in subjects self-reporting as other, 534.55 cells/µL (range: 0.01 to 2564.74 cells/µL•days) in Black or African American subjects, and 192.81 cells/µL•days (range: 0.00 to $1.65 \times 10^{4}$ cells/µL•days) in White subjects. The median time-to-peak was 8 days for all race groups.

*Ethnicity*

A total of 159 subjects were not Hispanic or Latino and 8 subjects were Hispanic or Latino. Subjects with ethnicity data not reported were excluded from the analysis.

Median peak anti-CD19 CAR T-cell levels were 26.24 cells/µL (range: 2.75 to 276.28 cells/µL) in Hispanic or Latino subjects and 25.52 cells/µL (range: 0.04 to 1173.25 cells/µL) in not Hispanic or Latino subjects. The median $AUC_{0-28}$ was 421.40 cells/µL•days (range: 22.38 to 3759.66 cells/µL•days) in Hispanic or Latino subjects and 232.38 cells/µL•days (range: 0.00 to $1.65 \times 10^{4}$ cells/µL•days) in not Hispanic or Latino subjects. The median time-to-peak was 8 days for both ethnicity groups.

*Baseline tumor burden*

Tumor burden was defined as the sum of the product of the longest diameters (SPD) of selected nodes or lesions using central assessment. Subjects without baseline tumor burden measurement were excluded from the analysis.

The median peak anti-CD19 CAR T-cell levels and $AUC_{0-28}$ values were similar between quartiles. The median peak anti-CD19 CAR T-cell levels were 23.46 cells/µL in the first (lowest) tumor burden quartile, 33.72 cells/µL in the second quartile, 27.11 cells/µL in the third quartile, and 30.71 cells/µL in the fourth (highest) quartile. Median values for $AUC_{0-28}$ were 276.50 cells/µL•days in the first quartile, 248.53 cells/µL•days in the second quartile, 314.73 cells/µL•days in the third quartile, and 240.08 cells/µL•days in the fourth quartile.

Pharmacokinetic parameters were summarized for 2 subgroups of subjects (n=77 per group) with baseline tumor SPD ≤ median as compared to subjects with SPD > median. The median peak anti-CD19 CAR T-cell levels were 25.52 cells/µL (range: 0.04 to 459.76 cells/µL) in subjects with baseline tumor SPD ≤ median and 29.03 cells/µL (range: 0.55 to 1173.25 cells/µL) for subjects with baseline tumor SPD > median. The median $AUC_{0-28}$ was 264.68 cells/µL•days (range: 0.00 to 6223.76 cells/µL•days) for subjects with baseline tumor SPD ≤ median and 281.45 cells/µL•days (range: 0.01 to $1.65 \times 10^{4}$ cells/µL•days) for subjects with baseline tumor SPD > median. The median time-to-peak was 8 days for all subgroups.

*Geographic region (US, Canada, Europe, Australia, Israel)*

A total of 132 subjects were treated in North America (US and Canada) and 38 subjects were treated in the Rest of the World (Europe, Australia, and Israel).

Median peak anti-CD19 CAR T-cell levels were 27.11 cells/µL (range: 0.04 to 1173.25 cells/µL) in the North America group and 22.41 cells/µL (range: 0.30 to 459.76 cells/µL) in the Rest of the World group. The median $AUC_{0-28}$ was 290.39 cells/µL•days (range: 0.00 to $1.65 \times 10^4$ cells/µL•days) in the North America group and 134.09 cells/µL•days (range: 3.99 to 6223.76 cells/µL•days) in the Rest of the World group. The median time-to-peak was 8 days for subjects treated in the North America group and 9 days for subjects treated in the Rest of the World group.

*Eastern Cooperative Oncology Group performance status*

A total of 92 subjects had an Eastern Cooperative Oncology Group Performance Status (ECOG) score of 0 and 78 subjects had an ECOG score of 1.

Median peak anti-CD19 CAR T-cell levels were 25.84 cells/µL (range: 0.04 to 1173.25 cells/µL) in subjects with an ECOG score of 0 and 26.02 cells/µL (range: 0.09 to 622.50 cells/µL) in subjects with an ECOG score of 1. The median $AUC_{0-28}$ was 236.00 cells/µL•days (range: 0.00 to $1.65 \times 10^4$ cells/µL•days) in subjects with an ECOG score of 0 and 236.23 cells/µL•days (range: 0.00 to 8541.63 cells/µL•days) in subjects with an ECOG score of 1. The median time-to-peak was 8 days for both subjects with an ECOG score of 0 and 1.

*Response to first-line therapy (refractory/relapsed subgroup)*

Using data derived from the clinical database for response to first-line therapy, 124 subjects were primary refractory to the first-line therapy, 26 subjects relapsed ≤ 6 months of completion of first-line therapy, and 20 subjects relapsed > 6 and ≤ 12 months of completion of first-line therapy.

Median peak anti -CD19 CAR T-cell levels were 27.38 cells/µL (range: 0.04 to 1173.25 cells/µL) in subjects who were primary refractory to the first-line therapy, 15.66 cells/µL (range: 0.55 to 276.28 cells/µL) in subjects who relapsed ≤ 6 months of completion of first-line therapy, and 25.14 cells/µL (range: 0.41 to 459.76 cells/µL) in subjects who relapsed > 6 and ≤ 12 months of completion of first-line therapy. The median $AUC_{0-28}$ was 279.16 cells/µL•days (range: 0.00 to $1.65 \times 10^4$ cells/µL•days) in subjects who were primary refractory to the first-line therapy, 167.81 cells/µL•days (range: $4.02 \times 10^{-3}$ to 3759.66 cells/µL•days) in subjects who relapsed ≤ 6 months of completion of first-line therapy, and 188.77 cells/µL•days (range: 5.30 to 6223.76 cells/µL•days) in subjects who relapsed > 6 and ≤ 12 months of completion of first-line therapy.

Anti-CD19 CAR T-cell levels were also evaluated by derived response to first-line therapy for the refractory group (n = 124) versus the overall relapse subgroup (≤ 12 months of completion of the first-line therapy, n = 46). Median peak anti-CD19 CAR T-cell levels were 16.13 cells/µL (range: 0.41 to 459.76 cells/µL) in subjects who relapsed ≤ 12 months of completion of first-line therapy. The median $AUC_{0-28}$ was 187.76 cells/µL•days (range: 4.02 ´ $10^{-3}$ to 6223.76 cells/µL•days) in subjects who relapsed ≤ 12 months of completion of first-line therapy. The median time-to-peak was 8 days for all first-line therapy subgroups.

*Disease type*

Per central laboratory assessment of disease type, 121 subjects had DLBCL and 28 subjects had HGBL. DLBCL included DLBCL NOS; primary cutaneous DLBCL, leg type DLBCL; $EBV^+$ DLBCL of the elderly; and T-cell/histiocyte-rich large cell lymphoma {Campo 2011}. HGBL included any LBCL (except follicular or lymphoblastic lymphoma) with *MYC*, *BCL2*, and/or *BCL6* rearrangements; and HGBL NOS {Swerdlow 2016}.

Median peak anti-CD19 CAR T-cell levels were 29.28 cells/µL (range: 0.88 to 242.74 cells/µL) in subjects with HGBL and 23.52 cells/µL (range: 0.04 to 1173.25 cells/µL) in subjects with DLBCL. The median $AUC_{0\text{-}28}$ was 394.10 cells/µL•days (range: 7.61 to 3362.34 cells/µL•days) in subjects with HGBL and 221.74 cells/µL•days (range: 0.00 to $1.65 \times 10^4$ cells/µL•days) in subjects with DLBCL. The median time-to-peak was 8 days in both subjects with DLBCL and with HGBL.

*Molecular subgroup*

Based on central laboratory assessment of molecular subgroups, 104 subjects had GCB, 14 subjects had ABC, and 17 subjects were unclassified (subjects with missing data are not included). Subjects with molecular subgroup reported as not applicable or missing by central laboratory assessment were excluded from the analysis.

Median peak anti-CD19 CAR T-cell levels were 25.37 cells/µL (range: 0.09 to 459.76 cells/µL) in subjects in the GCB molecular subgroup, 37.75 cells/µL (range: 0.83 to 622.50 cells/µL) in subjects in the ABC molecular subgroup, and 21.82 cells/µL (range: 1.69 to 128.58 cells/µL) in subjects unclassified. The median $AUC_{0\text{-}28}$ was 323.74 cells/µL•days (range: 0.00 to 6223.76 cells/µL•days) in subjects in the GCB molecular subgroup, 240.08 cells/µL•days (range: $4.02 \times 10^{-3}$ to 8541.63 cells/µL•days) in subjects in the ABC molecular subgroup, and 204.32 cells/µL•days (range: 6.22 to 1363.98 cells/µL•days) in subjects unclassified. The median time-to-peak was 8 days in subjects in the GCB, ABC, and unclassified molecular subgroups.

*Double-hit/triple-hit/double-expressor status*

Based on central laboratory assessment of HGBL double-hit (*C-MYC*, and either *BCL2* or *BCL6* rearrangements), HGBL triple-hit (*C-MYC*, *BCL2*, and *BCL6* rearrangements), double-expressor lymphoma (overexpression of *C-MYC* and *BCL2*), and *MYC* rearrangement status, 28 subjects had HGBL double-hit or triple-hit, 55 subjects had double-expressor lymphoma, and 13 subjects had *MYC* rearrangement. Subjects with a status of unclassified or not reported were excluded from the analysis.

Median peak anti-CD19 CAR T-cell levels were 32.33 cells/µL (range: 0.04 to 216.07 cells/µL) in subjects with *MYC* rearrangement, 29.28 cells/µL (range: 0.88 to 242.74 cells/µL) in subjects with HGBL double-hit or triple-hit lymphoma, and 21.77 cells/µL (range: 0.30 to 1173.25 cells/µL) in subjects with double-expressor lymphoma. The median $AUC_{0\text{-}28}$ was 444.44 cells/µL•days (range: 0.00 to 3852.87 cells/µL•days) in subjects with *MYC* rearrangement, 394.10 cells/µL•days (range: 7.61 to 3362.34 cells/µL•days) in subjects with HGBL double-hit or triple-hit lymphoma, and 187.76 cells/µL•days (range: $4.02 \times 10^{-3}$ to $1.65 \times 10^4$ cells/µL•days) in subjects with double-expressor lymphoma, and. The median time-to-peak was 8 days in subjects with HGBL double-hit or triple-hit, double-expressor lymphoma, and *MYC* rearrangement.

*CD19 positive status*

A total of 136 subjects were CD19 IHC positive ($CD19^+$) and 13 subjects were CD19 IHC negative ($CD19^-$). $CD19^+$ is defined as having an H-score ≥ 5. Subjects with missing CD19 H-scores were excluded from the analysis.

The median peak anti-CD19 CAR T-cell levels were 25.52 cells/µL (range: 0.04 to 622.50 cells/µL) in $CD19^+$ subjects and 22.62 cells/µL (range: 1.50 to 1173.25 cells/µL) in $CD19^-$ subjects. The median $AUC_{0\text{-}28}$ was 222.51 cells/µL•days (range: 0.00 to 8541.63 cells/µL•days) in $CD19^+$ subjects and 300.90 cells/µL•days (range: 5.17 to $1.65 \times 10^4$ cells/µL•days) in $CD19^-$ subjects. The median time-to-peak was 8 days in both subgroups ($CD19^+$ and $CD19^-$ subjects).

CD19 positive/negative status after disease progression was reported for 7 subjects. Three of 7 subjects were $CD19^-$ after disease progression.

Association between pharmacokinetic profile and clinical response outcomes

*Event-free survival*

The primary efficacy endpoint was event-free survival (EFS) with progression events and censoring using blinded central assessment. EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy, or death from any cause.

Of the 81 subjects who had > median anti-CD19 CAR T-cell levels, 44 subjects (54%) had an EFS event and 37 subjects (46%) were censored (did not have an EFS event or were lost to follow-up). Of the 81 subjects who had ≤ median anti-CD19 CAR T-cell level, 52 subjects (64%) had an EFS event and 29 subjects (36%) were censored.

A possible association between peak anti-CD19 CAR T-cell levels and EFS was observed when peak anti-CD19 CAR T-cell levels were categorized as ≤ median versus > median (hazard ratio [HR] stratified: 0.66; 95% confidence interval [CI]: 0.43, 0.99; stratified 1-sided log-rank p = 0.0210). A trend was also observed between $AUC_{0-28}$ and EFS (HR stratified: 0.77; 95% CI: 0.51, 1.16), but the stratified 1-sided log-rank p-value was 0.1010.

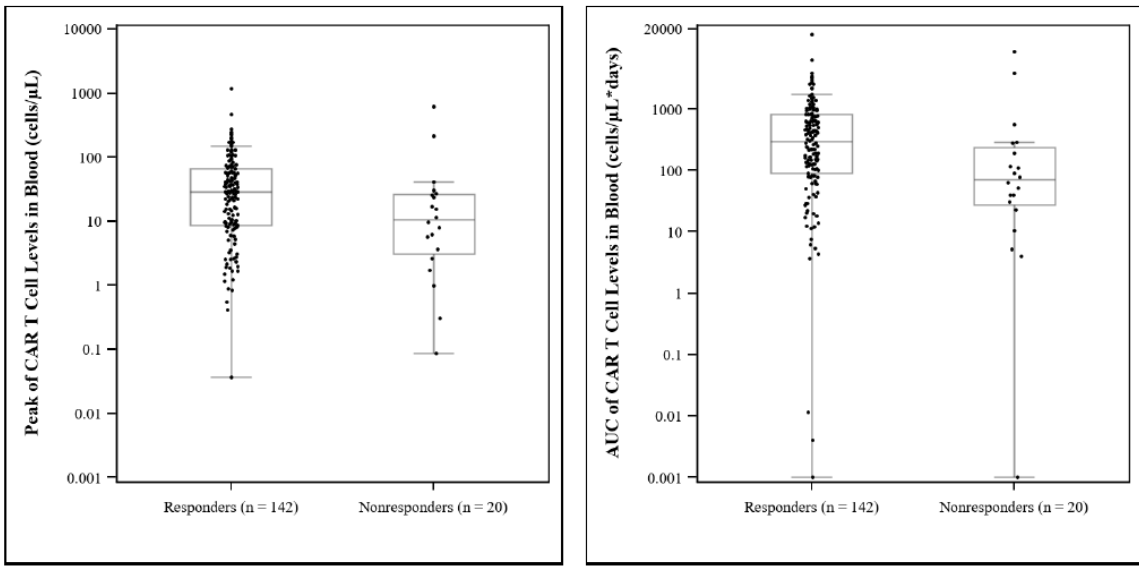
*Objective response*

Among 170 subjects who received axicabtagene ciloleucel, 149 subjects were responders (CR or partial response [PR]) and 21 subjects were nonresponders (stable disease [SD] or progressive disease [PD]).

Responders had numerically higher median anti-CD19 CAR T-cell peak and $AUC_{0-28}$ levels compared with nonresponders. The median peak anti-CD19 CAR T-cell level was 28.94 cells/µL (range: 0.04 to 1173.25 cells/µL) for responders versus 10.45 cells/µL (range: 0.09 to 622.50 cells/µL) for nonresponders (p = 0.0224). The median $AUC_{0-28}$ was 292.86 cells/µL•day (range: 0.00 to $1.65 \times 10^4$ cells/µL•day) for responders versus 70.14 cells/µL•days (range: 0.00 to 8541.63 cells/µL•day) for nonresponders (p = 0.0054).

Box plots of anti-CD19 CAR T-cell peak and $AUC_{0-28}$ levels in responders (subjects with a CR or PR) and non-responders (subjects with SD or PD) per central assessment are presented in the following Figure 2.

**Figure 2. Box Plot of Peak and $AUC_{0-28}$ of Anti-CD19 CAR T-Cell Levels in Blood by Objective Response per Central Assessment (Safety Analysis Set)**

2. 


Data cutoff date 18MAR2021. Abbreviation: AUC, area-under-the-curve; CAR, chimeric antigen receptor.

Notes: Responders are defined as subjects experiencing best response of partial or complete response; nonresponders are defined as subjects experiencing best response of stable or progressive disease. Peak is defined as the maximum number of CAR T cells in blood measured after the axicabtagene ciloleucel infusion. AUC is defined as the AUC in a plot of number of CAR T cells in blood against scheduled visit from Treatment day 0 to Week 4 post-treatment. Values of 0.001 in the Y-axis indicate values of zero. Only subjects in axicabtagene ciloleucel arm are included.

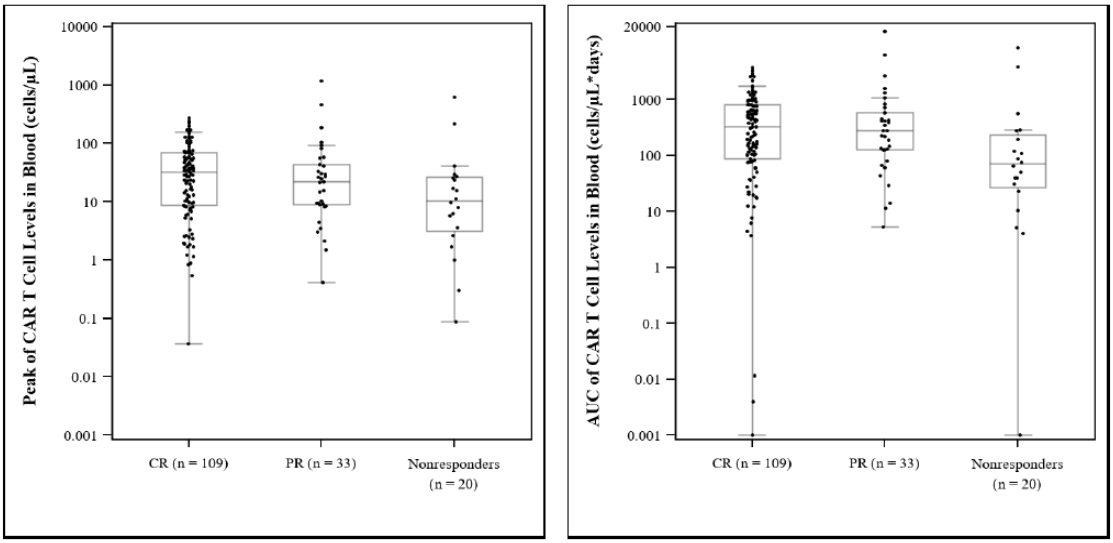
*Best overall response*

Among 162 evaluable subjects, 109 subjects achieved a best response of CR, 33 subjects achieved a best response of PR, and 20 subjects had a best response of SD or PD (nonresponders).

Subjects whose best response was CR had numerically higher anti-CD19 CAR T-cell peak and $AUC_{0-28}$ levels compared with subjects whose best response was PR or subjects who were nonresponders. The median peak anti-CD19 CAR T-cell level was 32.33 cells/µL (range: 0.04 to 276.28 cells/µL) for subjects who achieved CR, 22.30 cells/µL (range: 0.41 to 1173.25 cells/µL) for subjects who achieved PR, and 10.45 cells/µL (range: 0.09 to 622.50 cells/µL) for nonresponders (p = 0.0501). The median $AUC_{0-28}$ was 322.18 cells/µL•day (range: 0.00 to 3759.66 cells/µL•days) for subjects who achieved CR, 279.16 cells/µL•day (range: 5.30 to $1.65 \times 10^4$ cells/µL•days) for subjects who achieved PR, and 70.14 cells/µL•days (range: 0.00 to 8541.63 cells/µL•days) for nonresponders (p = 0.0201).

Boxplots for peak level and $AUC_{0-28}$ by best response category (CR, PR, or nonresponders) are presented in the following Figure 3.

**Figure 3. Box Plot of Peak and $AUC_{0-28}$ of Anti-CD19 CAR T-Cell Levels in Blood by Best Overall Response per Central Assessment (Safety Analysis Set)**

3. 


Data cutoff data = 18MAR2021. Abbreviation: AUC, area-under-the-curve; CAR, chimeric antigen receptor; CR, complete response; PR, partial response.

Notes: Nonresponders are defined as subjects experiencing best response of stable or progressive disease. Peak is defined as the maximum number of CAR T cells in blood measured after the axicabtagene ciloleucel infusion. AUC is defined as the AUC in a plot of number of CAR T cells in blood against scheduled visit from Treatment day 0 to Week 4 post-treatment. Values of 0.001 in the Y-axis indicate values of zero. Only subjects in axicabtagene ciloleucel arm are included.

*Ongoing response*

Among 154 evaluable subjects, 70 subjects were in ongoing response (defined as ongoing or complete or partial responses at data cutoff), 64 subjects had relapsed, and 20 subjects had no response.

Comparable anti-CD19 CAR T-cell peak and $AUC_{0-28}$ levels were observed between subjects who were in ongoing response and subjects who had relapsed, while the values were lower in subjects with no response. Specifically, the median peak anti-CD19 CAR T-cell level was 29.68 cells/µL (range: 0.55 to 276.28 cells/µL) in subjects with ongoing response, 27.44 cells/µL (range: 0.04 to 1173.25 cells/µL) for relapsed subjects, and 10.45 cells/µL (range: 0.09 to 622.50 cells/µL) in subjects with no response. The p-value for the overall comparison of peak values was p = 0.0713. The median $AUC_{0-28}$ was 276.88 cells/µL•days (range: $4.02 \times 10^3$, 3759.66 cells/µL•days) in subjects with ongoing response, 313.23 cells/µL•days (range: 0.00, $1.65 \times 10^4$ cells/µL•days) in relapsed subjects (p = 0.7190), and 70.14 cells/µL•days (range: 0.00 to 8541.63 cells/µL•days) in subjects with no response. The p-value for the overall comparison of $AUC_{0-28}$ values was p = 0.0205. Notably, $AUC_{0-28}$ was associated with ongoing response compared with nonresponse (p = 0.0250) and with relapsed disease compared with nonresponders (p = 0.0199).

*OS*

Of the 81 subjects who had > median peak anti-CD19 CAR T-cell levels, 31 subjects (38%) had an OS event (ie, death) per central assessment and 50 subjects (62%) were censored (did not have an OS event or were lost to follow-up). Of the 81 subjects who had ≤ median anti-CD19 CAR T-cell level, 31 subjects (38%) died and 50 subjects (62%) were censored.

No association between peak anti-CD19 CAR T-cell levels and OS was observed when peak anti-CD19 CAR T-cell levels were categorized as ≤ median versus > median (HR stratified: 0.84; 95% CI: 0.51, 1.40; stratified 1-sided log-rank p = 0.2537). Also, no association was observed between $AUC_{0-28}$ and OS (HR stratified: 0.87; 95% CI: 0.52, 1.46; stratified 1-sided log-rank p = 0.3018).

*Modified EFS*

Modified EFS (mEFS) was defined the same way as EFS, except that SD as the best response by the Study Day 150 assessment was not considered an event.

Of the 81 subjects who had > median anti-CD19 CAR T-cell level, 43 subjects (53%) had an event and 38 subjects (47%) were censored (did not have an event or were lost to follow-up). Of the 81 subjects who had ≤ median anti-CD19 CAR T-cell level, 49 subjects (60%) had an event, and 32 subjects (40%) were censored.

An association between peak anti-CD19 CAR T-cell levels and mEFS was observed when peak anti-CD19 CAR T-cell levels were categorized as ≤ median versus > median (HR stratified: 0.70; 95% CI: 0.46, 1.07; stratified 1-sided log-rank p = 0.0471). A similar trend was observed between $AUC_{0-28}$ and mEFS (HR stratified: 0.81; 95% CI: 0.53, 1.24), although the stratified 1-sided log-rank p-value was 0.1682.

*Progression-free survival*

Progression-free survival (PFS) was defined as the time from the randomization date to the date of disease progression or death from any cause per blinded central assessment. Subjects not meeting the criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the data cutoff date or new lymphoma therapy start date (including stem cell transplant in the axicabtagene ciloleucel arm or retreatment of axicabtagene ciloleucel), whichever was earlier.

Of the 81 subjects who had > median anti-CD19 CAR T-cell level, 40 subjects (49%) had an event and 41 subjects (51%) were censored (did not have an event or were lost to follow-up). Of the 81 subjects who had ≤ median anti-CD19 CAR T-cell level, 43 subjects (53%) had an event, and 38 subjects (47%) were censored.

An association between peak anti-CD19 CAR T-cell levels and PFS was observed when peak anti-CD19 CAR T-cell levels were categorized as ≤ median versus > median (HR stratified: 0.68; 95% CI: 0.44; 1.06; stratified 1-sided log-rank p = 0.0443). However, an association was not observed between $AUC_{0-28}$ and PFS (HR stratified: 0.81; 95% CI: 0.52, 1.26; stratified 1-sided log-rank p = 0.1737).

<u>Association between pharmacokinetics and safety outcomes</u>

*Association of pharmacokinetic parameters with CRS*

Among 170 subjects who received axicabtagene ciloleucel, 11 subjects had Grade 3 or higher CRS (10 subjects with evaluable samples for peak CAR T-cell levels and $AUC_{0-28}$ analyses) and 159 subjects had Grade 2, Grade 1, or no CRS (152 subjects with evaluable samples for peak CAR T-cell levels and $AUC_{0-28}$ analyses).

Numerically higher anti-CD19 CAR T-cell peak and $AUC_{0-28}$ levels were observed with Grade 3 or higher CRS, although there was no strong association. The median peak anti-CD19 CAR T-cell level was 2.08-fold higher for subjects with Grade 3 or higher CRS compared with subjects with Grade 2 or lower CRS (52.05 versus 25.04 cells/μL; p = 0.2040). The median $AUC_{0-28}$ was 1.77-fold higher for subjects with Grade 3 or higher CRS compared with subjects with Grade 2 or lower CRS (402.41 versus 227.45 cells/μL•days; p = 0.2494).

*Association of pharmacokinetic parameters with neurologic events*

Among 170 subjects who received axicabtagene ciloleucel, 36 subjects had Grade 3 or higher neurologic events (33 subjects with evaluable samples for peak CAR T-cell levels and $AUC_{0-28}$ analyses), and 134 subjects had Grade 2, Grade 1, or no neurologic events (129 subjects with evaluable samples for peak CAR T-cell levels and $AUC_{0-28}$ analyses).

Higher anti-CD19 CAR T-cell peak and $AUC_{0-28}$ levels were associated with Grade 3 or higher neurologic events. The median peak anti-CD19 CAR T-cell level was 2.60-fold higher for subjects with Grade 3 or higher neurologic events compared with subjects with Grade 2, Grade 1, or no neurologic events (57.93 versus 22.30 cells/µL; p = 0.0006). The median $AUC_{0-28}$ was 3.43-fold higher for subjects with Grade 3 or higher neurologic events compared with subjects with Grade 2, Grade 1, or no neurologic events (601.99 versus 175.44 cells/µL•days; p = 0.0004).

## 2.4.3. Pharmacodynamics

Methods

Serum analytes:

The serum analytes evaluated are known to be involved in mediating the antitumor activity of CAR T cells and treatment-related toxicity {Brudno 2018, Kochenderfer 2013, Kochenderfer 2017a, Neelapu 2017}. Levels of analytes (proinflammatory and immune-modulating cytokines, chemokines, effector molecules, and angiogenesis and acute phase proteins) were evaluated in serum samples at multiple time points. If the subject experienced a Grade 3 or higher axicabtagene ciloleucel-related toxicity such as Grade 3 cytokine release syndrome (CRS) or neurologic event, one additional blood draw for cytokines was to be taken at the time of the Grade 3 or higher axicabtagene ciloleucel-related toxicity and upon resolution of the event. Due to the timing of samples collected after infusion, the calculated values for peak, AUC, and time-to-peak are considered estimates.

Levels of the following 29 serum analytes are presented:

- Homeostatic/proliferative: interleukin (IL)-2, IL-7, and IL-15
- Inflammatory/immune-modulating: IL-1 receptor antagonist (IL-1RA), IL-2 receptor α (IL-2Rα), IL-4, IL-5, IL-6, IL-10, IL-12 P40, and granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Chemokine: C-X-C motif chemokine (CXCL) 10 (also known as interferon [IFN]-γ -induced protein-10 (IP-10), IL-8, IL-17, monocyte chemotactic protein (MCP)-1 (also known as C-C motif chemokine ligand [CCL]2), MCP-4, macrophage-derived chemokine (MDC), macrophage inflammatory protein (MIP)-1α, MIP-1β, and thymus and activation regulated chemokine (TARC)
- Immune effector: granzyme B, IFN-γ, and tumor necrosis factor (TNF)-α
- Acute phase proteins: C-reactive protein (CRP), ferritin, and serum amyloid A (SAA)
- Other analytes: intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and vascular endothelial growth factor (VEGF)
- IL-23 was evaluated but had no detectable values within the quantitative range and is therefore not described

Exploratory associations described are based on nominal Wilcoxon rank-sum $p \leq 0.05$. Multiplicity adjustment was not performed; therefore, p-values do not indicate statistical significance but rather a trend in association between analytes and treatment-related toxicity.

CFS analytes:

Levels of analytes (proinflammatory and immune-modulating cytokines, chemokines, effector molecules, and angiogenesis and acute phase proteins) were evaluated in cerebrospinal fluid (CSF) samples collected when subjects had new onset Grade 2 or higher neurologic symptoms after axicabtagene ciloleucel infusion. Due to the timing of samples collected after infusion, the calculated values for peak, AUC, and time-to-peak are considered estimates.

Postbaseline levels of the following 40 CSF analytes are presented:

- Homeostatic/proliferative: IL-2, IL-7, and IL-15
- Inflammatory/immune-modulating: eotaxin (also known as CCL11), eotaxin-3 (also known as CCL26), IL-1α, IL-1β, IL-1RA, IL-2Rα, IL-4, IL-5, IL-6, IL-10, IL-12 P40, IL-12 P70, IL-13, IL-16, IL-17, GM-CSF, programmed death-ligand 1 (PD-L1, also known as B7-H1), soluble Fas ligand, and TNF-β
- Chemokine: CXCL10 (IP-10), IL-8, MCP-1 (also known as CCL2), MCP-4, MDC, MIP-1α, MIP-1β, and TARC (also known as CCL17)
- Immune effector: granzyme A, granzyme B, IFN-γ, perforin, and TNF-α
- Acute phase proteins: CRP, ferritin, and SAA
- Other analytes: ICAM-1 and VCAM-1

B-cell evaluations:

To monitor the on-target/off-tumor effects of axicabtagene ciloleucel on CD19-expressing B cells, the presence and percentage of $CD19^+$, $CD20^+$, or $CD19^+CD20^+$ B cells in cryopreserved PBMCs were evaluated by a flow cytometry assay. Results are presented as the percentage of B cells in viable $CD45^+$ leukocytes. The limit of detection and LLOQ were determined to establish the sensitivity of the assay. This assay does not distinguish between normal and malignant $CD19^+$ B cells.

Product T cell phenotype and Markers of T-cell exhaustion in product:

T cell phenotype (CCR7 Vs CD45RA) and exhaustion markers (e.g. PD-1, TIM-3, LAG-3) with respect to both $CAR^{+/-}$ populations were assayed in the products. Viable $CD3^+$ T cells from cryopreserved preinfusion axicabtagene ciloleucel product retains were immunophenotyped at the single cell level, using specific antibody panels in multiparametric flow cytometry.

**Pharmacodynamics results**

Pharmacodynamics in serum

Key observations included the following:

- On Treatment day 0, after lymphodepleting chemotherapy and on the day of the axicabtagene ciloleucel infusion, median serum levels of IL-15 and MCP-1 increased by ≥ 2-fold and median serum levels of granzyme B, IL-12 P40, IL-17, and MDC decreased by ≥ 2-fold relative to baseline levels. Median serum levels of the other 23 analytes had < 2-fold change after lymphodepletion relative to baseline.
- On Treatment day 1 after infusion of axicabtagene ciloleucel, median serum levels of 6 of 29 analytes had ≥ 2-fold increase from Treatment day 0: IFN-γ, IL-2, IL-5, IL-6, IL-10, and IL-17. Also, 9 of 29 analytes had a ≥ 2-fold increase on Treatment day 1 relative to baseline (IFN-γ, IL-2, IL-5, IL-6, IL-10, IL-15, IL-17, MCP-1, and SAA), while granzyme B and MDC had a ≥ 2-fold decrease on Treatment day 1 relative to baseline.

- On Treatment day 3 after infusion of axicabtagene ciloleucel, median serum levels of 18 of 29 analytes had < 2-fold change relative to baseline, while 10 analytes were elevated by ≥ 2-fold relative to baseline (CRP, IFN-γ, IL-2, IL-5, IL-6, IL-10, IL-15, IL-17, MCP-1, and SAA). On Treatment day 3, MDC was decreased by ≥ 2-fold relative to baseline, but this was likely due to lymphodepleting chemotherapy. Also, compared with Treatment day 0, median serum levels on Treatment day 3 had < 2-fold change in 19 of 29 analytes, while 11 analytes were elevated by ≥ 2-fold (CRP, granzyme B, IFN-γ, IL-2, IL-5, IL-6, IL-10, IL-12 P40, IL-17, SAA, and TARC).
- On Treatment day 7 after infusion of axicabtagene ciloleucel, median serum levels of 14 of the 29 analytes had < 2-fold change relative to baseline, while 14 analytes were elevated by ≥ 2-fold relative to baseline (CRP, CXCL10, ferritin, granzyme B, IFN-γ, IL-2, IL-2 Rα, IL-5, IL-6, IL-8, IL-10, IL-15, SAA, and TARC). On Treatment day 7, MDC was decreased by ≥ 2-fold relative to baseline, but this was likely due to lymphodepleting chemotherapy. Also, compared with Treatment day 0, median serum levels on Treatment day 7 had < 2-fold change in 16 of 29 analytes, while 13 analytes were elevated by ≥ 2-fold (CRP, CXCL10, granzyme B, IFN-γ, IL-2, IL-2 Rα, IL-5, IL-6, IL-8, IL-10, IL-17, SAA, and TARC). On Treatment day 7, MCP-1 was decreased by ≥ 2-fold relative to Treatment day 0.
- The median time-to-peak for 19 of 29 analytes was 8 days (ie, 7 days after infusion of axicabtagene ciloleucel). The median time-to-peak was 1 day for IL-4; 2 days for GM-CSF, IL-2, IL-7, IL-15, IL-17, MCP-1, and MIP-1β; 4 days for SAA; and 5 days for MCP-4. Most analytes were elevated by ≥ 2-fold at peak compared with baseline in ≥ 50% of subjects (exceptions: ICAM-1, IL-4, IL-7, IL-12 P40, MCP-4, MDC, MIP-1α, MIP-1β, TNF-α, VCAM-1, and VEGF).
- By Week 4 post-treatment, the majority of the serum analytes had returned to near baseline levels; 9 of 29 analytes remained elevated by 2-fold or more in ≥ 20% of subjects (CXCL10, ferritin, granzyme B, IFN-γ, IL-2, IL-6, IL-10, IL-15, and IL-17).

Pharmacodynamics in CSF

Analytes in the CSF were analyzed following treatment with axicabtagene ciloleucel in subjects who had Grade 2 or higher neurologic events (n = 13).

All subjects had detectable levels of the following CSF analytes: CRP, CXCL10, eotaxin-1, ferritin, ICAM-1, IL-1 RA, IL-2Rα, IL-6, IL-8, MCP-1, MIP-1β, PD-L1, TARC, TNF-α, and VCAM-1. Eight of the 40 analytes were below the limit of quantification (granzyme A, IL-1α, IL-1β, IL-4, IL-12 P40, IL-12 P70, IL-13, MDC and TNF-β).

B-cell recovery in blood

In the safety analysis set, 81 of 141 tested subjects had detectable B cells at baseline (before initiation of lymphodepleting chemotherapy and axicabtagene ciloleucel infusion), with a median B-cell level of 0.27% of viable leukocytes (range: 0.02% to 32.18%). At Month 3, the first time point at which B cells were measured after axicabtagene ciloleucel infusion, 52 of 138 tested subjects had detectable B cells, and the median B-cell level was 0.37% (range: 0.02% to 24.51%). With limited evaluable samples (n = 17), there was an indication of some B-cell recovery at Month 6, when the majority of samples still had undetectable B cells, but among the 7 subjects with detectable B cells, the median value was 4.02% (range: 0.04% to 23.00%). B cell recovery was clearer at Month 9 with the majority of subjects presenting detectable B-cell levels and a median detectable level of 9.79%. Recovery continued through Month 24, at which time 22 of 26 evaluable subjects had detectable B cells.

**Table 1. B-cell Levels Following Axicabtagene Ciloleucel Infusion (Safety Analysis Set)**

| **B-cell Levels (%)[a]** | **Axicabtagene Ciloleucel (N = 170)** |
|---|---|
| Baseline | |
| n | 141 |
| n (B cells below LLOQ) | 60 |
| n (B cells detectable) | 81 |
| Mean (STDEV) | 2.43 (5.09) |
| Median (Q1, Q3) | 0.27 (0.05, 2.00) |
| Min, Max | 0.02, 32.18 |
| 3 Months Post-treatment | |
| n | 138 |
| n (B cells below LLOQ) | 86 |
| n (B cells detectable) | 52 |
| Mean (STDEV) | 3.62 (6.67) |
| Median (Q1, Q3) | 0.37 (0.06, 3.22) |
| Min, Max | 0.02, 24.51 |
| 6 Months Post-treatment | |
| n | 17 |
| n (B cells below LLOQ) | 10 |
| n (B cells detectable) | 7 |
| Mean (STDEV) | 8.26 (8.98) |
| Median (Q1, Q3) | 4.02 (0.13, 17.65) |
| Min, Max | 0.04, 23.00 |
| 9 Months Post-treatment | |
| n | 77 |
| n (B cells below LLOQ) | 32 |
| n (B cells detectable) | 45 |
| Mean (STDEV) | 12.37 (12.47) |
| Median (Q1, Q3) | 9.79 (0.17, 22.75) |
| Min, Max | 0.02, 49.60 |
| 12 Months Post-treatment | |

| B-cell Levels (%)[a] | Axicabtagene Ciloleucel (N = 170) |
|---|---|
| n | 73 |
| n (B cells below LLOQ) | 34 |
| n (B cells detectable) | 39 |
| Mean (STDEV) | 15.95 (13.44) |
| Median (Q1, Q3) | 14.56 (1.35, 23.76) |
| Min, Max | 0.04, 52.88 |
| 18 Months Post-treatment | |
| n | 61 |
| n (B cells below LLOQ) | 22 |
| n (B cells detectable) | 39 |
| Mean (STDEV) | 17.75 (13.06) |
| Median (Q1, Q3) | 16.03 (7.90, 27.17) |
| Min, Max | 0.03, 54.77 |
| 24 Months Post-treatment | |
| n | 26 |
| n (B cells below LLOQ) | 4 |
| n (B cells detectable) | 22 |
| Mean (STDEV) | 19.99 (14.86) |
| Median (Q1, Q3) | 18.55 (12.49, 28.96) |
| Min, Max | 0.02, 48.99 |

Data cutoff date = 18MAR2021.

Abbreviations: LLOQ, lower limit of quantification; Max, maximum; Min, minimum; Q, quartile; STDEV, standard deviation.

Notes: Statistical analysis is based on levels of detectable B cells. Samples that failed to meet predefined assay criteria were excluded from the analysis. All time points are relative to the day of the axicabtagene ciloleucel infusion (ie, Treatment day 0) and include a window period.

a B-cell levels are given as a percentage representing the number of CD19+, CD20+, or CD19+CD20 + B cells relative to viable CD45 leukocytes.

Product attributes based on exhausted T-cell markers

Within the viable T-cell fraction ($CD3^+$ cells), the percentage of each subpopulation was assessed by flow cytometry by gating on the surface biomarkers. All cell populations are reported as % of T cell population.

The median percentage of $CAR^+$ T cells among notable markers is provided below:

- $CAR^+$ cells that expressed programmed cell death protein-1 (PD-1): 47.37% (12.06% to 81.02%).
- $CAR^+$ cells that expressed PD-1 and T-cell immunoglobulin and mucin domain-3 (TIM-3): 26.68% (7.09% to 50.60%).
- $CAR^+$ $T_{naïve}$ cells ($CCR7^+CD45RA^+$) that were $CD27^+CD28^+$: 11.67% (0.67% to 39.58%).
- $CAR^+$ $T_{em}$ cells ($CCR7^-CD45RA^-$) that were $CD27^-CD28^+$ and expressed PD-1: 5.63% (0.05% to 27.74%).
- $CAR^+$ $T_{eff}$ cells ($CCR7^-CD45RA^-$) that were $CD27^+CD28^+$ and expressed PD-1: 5.15% (0.02% to 20.56%).
- $CAR^+$ cells that expressed PD-1 and lymphocyte-activation gene-3 (LAG-3) (double expressors): 1.73% (0.34% to 14.41%).
- $CAR^+$ $T_{cm}$ cells ($CCR7^+CD45RA^-$) that were $CD27^+CD28^+$ and expressed PD-1: 1.66% ($5.24 \times 10^{-3}$% to 6.14%).
- $CAR^+$ cells that expressed PD-1, LAG-3, and TIM-3 (triple expressors): 1.57% (0.31% to 13.03%).
- Other CAR+ subsets reported values < 1% of total T-cell populations.

Association of serum pharmacodynamic parameters with CRS

Of the 29 serum analytes, the peak levels for the following analytes were nominally higher ($p \leq 0.05$) among subjects who experienced Grade 3 or higher CRS (n = 11) versus Grade 2, Grade 1, or no CRS (n = 159) after infusion of axicabtagene ciloleucel: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IL-2Rα, IL-6, IL-10, IL-15, IL-17, MCP-1, and VCAM-1. The following analytes presented nominally higher ($p \leq 0.05$) in AUC values among subjects who experienced a Grade 3 or higher CRS versus Grade 2, Grade 1, or no CRS after infusion of axicabtagene ciloleucel: ferritin, GM-CSF, granzyme B, IL-2Rα, IL-6, IL-15, IL-17, and VCAM-1. CXCL10, ICAM-1, MCP-1, and IL-10 had nominally higher peak levels but not nominally higher AUC values. In addition, VEGF presented nominally higher in AUC, but not nominally higher in peak levels in subjects who experienced Grade 3 or higher CRS.

At baseline, the serum levels for the following analytes were nominally higher ($p \leq 0.05$) among subjects who experienced Grade 3 or higher CRS versus Grade 2, Grade 1, or no CRS after infusion of axicabtagene ciloleucel: IL-2Rα, IL-15, TNF-α, and VCAM-1.

At Treatment day 0, the serum levels for the following analytes were nominally higher ($p \leq 0.05$) among subjects who experienced Grade 3 or higher CRS versus Grade 2, Grade 1, or no CRS after infusion of axicabtagene ciloleucel: IL-2Rα, MCP-4, MDC, and VCAM-1.

The 3 analytes with the greatest fold change in median peak serum levels by grade of CRS were:

- IL-6 (median ratio: 3.5)
- GM-CSF (median ratio: 3.4)
- IL-10 (median ratio: 3.0)

Association of serum pharmacodynamic parameters with neurologic events

Of the 29 analytes, the median peak levels for the following analytes were nominally higher ($p \leq 0.05$) among subjects who experienced a Grade 3 or higher neurologic event (n = 36) versus Grade 2,

Grade 1, or no neurologic event (n = 134) after infusion of axicabtagene ciloleucel: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IFN-γ, IL-2, IL-2Rα, IL-5, IL-6, IL-10, IL-15, and VCAM-1. The following analytes presented nominally higher ($p \leq 0.05$) in AUC values among subjects who experienced a Grade 3 or higher neurologic event versus Grade 2, Grade 1, or no neurologic event after infusion of axicabtagene ciloleucel: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IFN-γ, IL-2Rα, IL-6, IL-10, IL-15, and VCAM-1. IL-2 and IL-5 had nominally higher peak levels but not nominally higher AUC values.

At baseline, the serum levels of only VCAM-1 were nominally higher ($p \leq 0.05$) among subjects who experienced a Grade 3 or higher neurologic event versus Grade 2, Grade 1, or no neurologic event after infusion of axicabtagene ciloleucel.

At Treatment day 0, the serum levels for the following analytes were nominally higher ($p \leq 0.05$) among subjects who experienced a Grade 3 or higher neurologic event versus Grade 2, Grade 1, or no neurologic event after infusion of axicabtagene ciloleucel: CRP, ICAM-1, IL-2Rα, IL-15, SAA, and VCAM-1.

The 4 analytes with the greatest fold change in median peak serum levels by grade of neurologic events were:

- IL-6 (median ratio: 2.4)
- IL-10 (median ratio: 2.3)
- GM-CSF (median ratio: 2.2)
- IL-5 (median ratio: 2.2)

Association of CSF pharmacodynamic parameters with neurologic events

Levels of 40 analytes in the CSF were evaluated for potential associations with grade of neurologic events following treatment with axicabtagene ciloleucel. CSF Samples and data were available for only 13 subjects (6 subjects who had Grade 3 or higher neurologic events and 7 subjects who had Grade 2 or lower neurologic events). Accordingly, there is limited insight from the results.

The following CSF analytes had median values that were ≥ 2-fold higher among subjects who experienced Grade 3 or higher neurologic event versus subjects who experienced Grade 2, Grade 1, or no neurologic event after infusion of axicabtagene ciloleucel: CRP, ferritin, granzyme B, IFN-γ, IL-2Rα, MCP-1, and SAA. Also, CRP, ferritin, granzyme B, IFN-γ, and IL-2Rα had a maximum value that was higher among subjects who experienced Grade 3 or higher neurologic event compared with subjects who experienced a Grade 2, Grade 1, or no neurologic event.

Association of product characteristics and clinical efficacy

A possible trend towards higher ORR (95% versus 80%, respectively) was observed for subjects whose products had a higher percentage (> the median value) of $CD3^+$ cells compared with those whose products had a lower percentage (≤ the median percentage) of $CD3^+$ cells. The reverse trend was observed for the percentage of $CD3^-$ cells, with a lower ORR (80% versus 95%, respectively) observed for subjects whose products had a higher percentage of $CD3^-$ cells compared with those whose products had a lower percentage $CD3^-$ cells.

A possible trend towards higher best overall response of CR (78% versus 57%, respectively) was observed for subjects whose products had a higher percentage (> the median value) of $CD3^+$ cells compared with those whose products had a lower percentage (≤ the median percentage) of $CD3^+$ cells.

The reverse trend was observed for the percentage of $CD3^-$ cells, with a lower best overall response of CR (57% versus 78%, respectively) observed for subjects whose products had a higher percentage of $CD3^-$ cells compared with those whose products had a lower percentage of $CD3^-$ cells.

Across all other product characteristic subgroups, the median best overall response of CR ranged from 59% to 76% and were generally consistent with the median best overall response of CR of 68% for the overall population.

A possible trend towards higher ongoing response rate at data cutoff (55% versus 31%, respectively) was observed for subjects whose products had a higher percentage (> the median value) of $T_{naïve}$ cells compared with those whose products had a lower percentage (≤ the median percentage) of $T_{naïve}$ cells. The reverse trend was observed for the percentage of $T_{em}$ cells, with a lower ongoing response rate at data cutoff (32% versus 55%, respectively) observed for subjects whose products had a higher percentage of $T_{em}$ cells compared with those whose products had a lower percentage of $T_{em}$ cells.

Across all other product characteristic subgroups, the ongoing response rates ranged from 35% to 52% and were generally consistent with the ongoing response rate of 44% for the overall population at data cutoff.

Association of product characteristics and safety outcomes

Preinfusion product characteristics were evaluated in subgroup analyses for the following treatment-emergent AE (TEAE) categories within the safety analysis set: all TEAEs, serious TEAEs, TEAEs and serious TEAEs deemed related to axicabtagene ciloleucel, CRS, neurologic events, serious neurologic events, cytopenias by lineage (thrombocytopenia, neutropenia, and anemia), infections, and serious infections.

The following key trends were observed for associations of product characteristics with TEAEs of interest:

- A higher incidence of Grade 3 or higher CRS was observed in subjects who received products that produced higher levels of IFN-γ (12% versus 1%, respectively).
- Higher incidences of Grade 3 or higher CRS or neurologic events were observed in subjects who were infused with a higher total number of $T_{em}$ plus $T_{eff}$ ($CCR7^-$) cells (31% versus 14%) or products that produced higher levels of IFN-γ (33% versus 15%).
- Higher incidences of Grade 3 or higher neurologic events were observed in subjects who were infused with a higher total number of $T_{em}$ cells (27% versus 13%), a higher total number of $T_{em}$ plus $T_{eff}$ ($CCR7^-$) cells (30% versus 10%), or products that had a higher percentage of $T_{eff}$ cells (27% versus 13%).
- Higher incidences of Grade 3 or higher serious neurologic events were observed in subjects who were infused with a higher total number of CD3 cells (19% versus 8%), a higher total number of CD8 cells (19% versus 8%), a higher total number of $T_{em}$ plus $T_{eff}$ ($CCR7^-$) cells (22% versus 6%), or products that produced higher levels of IFN-γ (21% versus 9%).

## 2.4.4. Discussion on clinical pharmacology

The pharmacokinetic and pharmacodynamic results on axicabtagene ciloleucel measurables and clinical parameters on safety and efficacy are in line with current scientific knowledge on the pharmacology of CAR T cells. The pharmacokinetic profile of axicabtagene ciloleucel in the ZUMA-7 trial presents a rapid expansion of CAR T cells peaking on Day 8 followed by a rapid contraction up to Week 4 and subsequent

low level persistence up to 18 to 24 months, consistent with the pharmacokinetic profile observed in the other trials with these CAR-T cells. The median time-to-peak was 8 days for all subgroup populations.

CAR T-cell expansion was associated with efficacy endpoints, and the pharmacokinetic associations with toxicity are consistent with previous observations with axicabtagene ciloleucel. There is no sex or age related difference in the median time-to-peak of 8 days. In addition, the median peak anti CD19 CAR T-cell levels are similar and not influenced by age or sex. Interestingly, there is no significant difference in median peak anti-CD19 CAR T-cell levels and median time-to-peak between CD19 positive and negative patients.

Higher anti-CD19 CAR T-cell levels were associated with subjects who were responders compared with subjects who were nonresponders. Median anti-CD19 CAR T cell peak and AUC0-28 were numerically higher in subjects whose best response was CR compared with subjects whose best response was PR. Higher anti-CD19 CAR T-cell levels in blood were associated with Grade 3 or higher neurologic events. Higher anti-CD19 CAR T-cell levels were observed in subjects who experienced Grade 3 or higher CRS.

Quantification of serum analytes revealed a rapid and transient increase in several proinflammatory and immune-modulatory analytes following infusion of axicabtagene ciloleucel, which is consistent with the known mechanism of action of anti-CD19 CAR T-cell therapy. The median time-to-peak for 19 of 29 serum analytes was 8 days (ie, 7 days after the day of the axicabtagene ciloleucel infusion). The median time-to-peak was 1 day for IL-4; 2 days for GM-CSF, IL-2, IL-7, IL-15, IL-17, MCP-1, and MIP-1β; 4 days for SAA; and 5 days for MCP-4. By Week 4 post-treatment, the majority of the serum analytes had returned to near baseline levels. Of the 29 serum analytes, the peak levels for the following analytes were nominally higher (nominal Wilcoxon rank sum $p \leq 0.05$) among subjects who experienced Grade 3 or higher CRS (n = 11) versus Grade 2, Grade 1, or no CRS (n = 159) after infusion of axicabtagene ciloleucel: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IL-2Rα, IL-6, IL-10, IL-15, IL-17, MCP-1, and VCAM-1. Of the 29 serum analytes, the peak levels for the following analytes were nominally higher (nominal Wilcoxon rank sum $p \leq 0.05$) among subjects who experienced a Grade 3 or higher neurologic event (n = 36) versus Grade 2, Grade 1, or no neurologic event (n = 134) after infusion of axicabtagene ciloleucel: CXCL10, ferritin, GM-CSF, granzyme B, ICAM-1, IFN-γ, IL-2, IL-2Rα, IL-5, IL-6, IL-10, IL-15, and VCAM-1. CSF levels of CRP, ferritin, granzyme B, IFN-γ, IL-2Rα, MCP-1, and SAA were ≥ 2 fold higher among subjects who experienced Grade 3 or higher neurologic event (n = 6) versus subjects who experienced Grade 2, Grade 1, or no neurologic event (n = 7) after infusion of axicabtagene ciloleucel.

Before lymphodepleting chemotherapy and axicabtagene ciloleucel infusion (baseline), B-cell levels were generally low (possibly due to first-line therapy, R-CHOP) with median levels < 1% of total leukocytes (median = 0.27), but detectable in the majority of subjects (81 of 141 tested subjects). After axicabtagene ciloleucel infusion, at Month 3, B-cell levels were undetectable in most subjects (86 of 138 tested subjects) and generally demonstrated recovery by Month 9 in subjects with evaluable samples.

## 2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics and pharmacodynamics results are presented extensively throughout the documentation. These results correlate well to previous observations with axicabtagene ciloleucel and are in line with the current scientific knowledge for the pharmacology characteristics of CAR T cells.

## *2.5. Clinical efficacy*

### 2.5.1. Main study

### Title of Study

A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)

### *Methods*

ZUMA-7 is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus SOCT in adult subjects with r/r LBCL. Adult subjects with r/r LBCL after first-line rituximab and anthracycline-based chemotherapy were randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOCT. Randomization was stratified by response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy, or relapse > 6 and ≤ 12 months of first-line therapy) and sAAIPI (0 to 1, or 2 to 3), as assessed at the time of screening.

For subjects in the axicabtagene ciloleucel arm, treatment consisted of lymphodepleting chemotherapy followed by a single intravenous infusion of axicabtagene ciloleucel. Bridging therapy of corticosteroids was allowed prior to lymphodepleting chemotherapy for subjects with high disease burden, at the discretion of the investigator. For subjects in the SOCT arm, treatment consisted of a single protocol-defined, platinum-based salvage chemotherapy regimen as selected by the treating investigator. Subjects who responded to salvage chemotherapy were to proceed to HDT with or without total body irradiation (TBI), followed by auto-SCT.

Disease response and progression were evaluated per the Lugano Classification {Cheson 2014}, by blinded central assessment and by the investigator. Subjects in both treatment arms were to be assessed for response and progression at the same times relative to randomization (Study Day 0): Study Days 50, 100, 150, and Month 9, then every 3 months thereafter until Month 24, and then every 6 months from Months 30 to 60. For a subject who completed the long-term follow-up period, the study was to take approximately 5 or 15 years to complete as determined by randomization to the SOCT or axicabtagene ciloleucel arms, respectively.

The primary analysis of EFS was conducted on the full analysis set (FAS), defined as all randomized subjects, and according to the randomized treatment regardless of whether study treatment was received, when all subjects had the opportunity to be followed for the Month 9 disease assessment (ie, the Month 9 timepoint had passed for all subjects) and 250 EFS events by blinded central assessment had been observed.

### *Study participants*

Approximately 350 subjects were randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOCT. Randomization was stratified by response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy, or relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted IPI (0 to 1, or 2 to 3), as assessed at the time of screening.

Key eligibility criteria included the following:

- Histologically proven LBCL including the following types defined by the WHO in 2016 {Swerdlow 2016}:
  - DLBCL not otherwise specified (including ABC/GCB)
  - HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement
  - DLBCL arising from follicular lymphoma
  - T-cell/histiocyte rich LBCL
  - DLBCL associated with chronic inflammation
  - Primary cutaneous DLBCL, leg type
  - Epstein-Barr virus$^{+}$ DLBCL
- Relapsed or refractory disease after first-line chemoimmunotherapy.
  - Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse ≤ 12 months of therapy.
  - Refractory disease defined as no complete remission to first-line therapy; subjects who were intolerant to first-line therapy were excluded.
- Received adequate first-line therapy including at a minimum:
  - Anti-CD20 monoclonal antibody unless the investigator determined the tumor was CD20 negative, and
  - An anthracycline-containing chemotherapy regimen
- Intended to proceed to HDT-auto-SCT if there was a response to second-line therapy
- Had radiographically documented disease
- No known history or suspicion of central nervous system involvement by lymphoma
- At least 2 weeks or 5 half-lives, whichever was shorter, had elapsed since any prior systemic cancer therapy at the time the subject provided consent
- Age 18 years or older at the time of informed consent

## *Treatments*

Axicabtagene ciloleucel arm:

Axicabtagene ciloleucel was administered after a 3-day lymphodepleting chemotherapy regimen consisting of fludarabine 30 mg/m$^2$/day and cyclophosphamide 500 mg/m$^2$/day, followed by 2 rest days. A single infusion of axicabtagene ciloleucel was administered intravenously at a target dose of 2 x $10^6$ anti-CD19 CAR T cells/kg (minimum dose of 1 x $10^6$ anti-CD19 CAR T cells/kg; for subjects weighing > 100 kg, the maximum flat dose was 2 x $10^8$ anti-CD19 CAR T cells).

Bridging therapy with corticosteroids was allowed prior to lymphodepleting chemotherapy at the discretion of the investigator for disease temporalization, but chemoimmunotherapy was not allowed as bridging therapy because of possible disease-modifying effects that would confound the short- and longterm disease assessments in the axicabtagene ciloleucel arm. Bridging therapy was to consist of corticosteroids (eg, dexamethasone at a dose of 20 to 40 mg or equivalent, either orally [PO] or IV daily for 1 to 4 days) administered after leukapheresis through 5 days before administration of axicabtagene ciloleucel.

SOCT arm:

Protocol-defined salvage chemotherapy regimens were: R-ICE, R-DHAP/R-DHAX, R-ESHAP, or R-GDP as selected by the treating investigator, administered every 2 to 3 weeks for 2 to 3 cycles. Subjects responding to salvage chemotherapy after 2 or 3 cycles were to proceed with HDT-auto-SCT per institutional or regional standards. Subjects not responding to salvage chemotherapy could receive additional treatment off protocol.

## *Objectives*

The primary objective was to determine if axicabtagene ciloleucel is superior to SOCT as measured by EFS, as determined by blinded central assessment.

Key secondary objectives were to evaluate the effect of axicabtagene ciloleucel compared with SOCT on ORR (determined by blinded central assessment), OS, PFS (determined by investigator assessment), and DOR and duration of CR among responding subjects (determined by blinded central assessment), and to evaluate the safety and effect of PROs and QoL of axicabtagene ciloleucel compared with SOCT.

## *Outcomes/endpoints*

Primary endpoint:

- EFS (with progression events and censoring) per blinded central assessment.

Key secondary endpoints:

- ORR per blinded central assessment
- OS

Other secondary endpoints:

- EFS (with progression and censoring events) based on investigator disease assessments
- PFS (with progression and censoring events) based on investigator disease assessments
- DOR by blinded central assessments
- Modified EFS
- Incidence of adverse events and clinically significant changes in safety laboratory test values, including antibodies to axicabtagene ciloleucel
- Changes from screening in the global health status QoL scale and the physical functioning domain of the EORTC QLQ-C30[a]
- Changes from screening in the EQ-5D-5L index and VAS scores[a]

Key exploratory endpoints:

- For axicabtagene ciloleucel treatment arm only: Levels of cytokines in the serum and levels of anti-CD19 CAR T cells in blood

Subgroups examined for efficacy and safety endpoints:

- Geographic region
- ECOG performance status at screening
- Age at randomization
- Sex
- Race/ethnicity
- Response to first-line therapy
- sAAIPI at time of screening
- Disease type
- Molecular subgroup (not assessed for safety endpoints)
- Double- or triple-hit status or double expressor status (not assessed for safety endpoints)

## *Sample size*

The study was planned to have an overall alpha of 2.5% with 1-sided testing. To preserve the overall significance level, statistical testing of the primary and key secondary efficacy endpoints was to follow a hierarchical testing scheme of EFS, followed by ORR and then OS (see "Statistical Methods" below). Overall 350 subjects were planned to be randomized (175 subjects per arm).

An EFS hazard ratio (test/control arm) of 0.67 was hypothesized in the FAS set, which corresponds to a median EFS of 4 versus 6 months (control vs test arm). The primary analysis was planned when 250 EFS events had been observed; the study was been sized to achieve approximately 90% power at the 1-sided 2.5% significance level to detect a 50% improvement in EFS. The EFS analyses was planned as event-driven and was to occur when the required number of events have been observed.

For the analysis of ORR, response rates of 36% and 78% in the control and test arms were assumed. ORR was to be tested with a stratified (randomization factors) Cochran-Mantel-Haenszel test at the 2.5% level among subjects with measurable disease at baseline.

An OS hazard ratio of 0.73 was hypothesized in the FAS set, which corresponds to a median OS of 15.8 versus 21.6 months (control vs test arm). The primary OS analysis was planned when approximately 210 deaths had been observed, but no later than 5 years after the first subject was randomized. Two interim analyses were planned for OS with the first interim analysis occurring at the time of primary EFS analysis and the second interim analysis when approximately 160 deaths have been observe, but no later than 4 years after the first subject was randomized.

## *Randomisation*

Once eligibility into the study had been confirmed, subjects were to be randomized in a 1:1 ratio to receive axicabtagene ciloleucel or investigator choice of standard of care chemotherapy as assigned by the interactive voice/web response system (IXRS). Randomization was to be stratified by response to first-line therapy (primary refractory, vs relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted IPI (0 to 1 vs 2 to 3) as assessed at the time of screening.

## *Blinding (masking)*

The study was planned as an open-label study where subjects and investigators were aware of the treatment received. Disease response and progression were evaluated per the Lugano Classification, by blinded central assessment and by the investigator.

Data handling procedures were to be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures were to be outlined in the study statistical analysis plan and Trial Integrity Document (TID). According to the TID, biostatisticians and biostatistical programmers from the sponsor had access to the restricted data at all time. However, access of the Sponsor's team to treatment allocation (and to corresponding variables such as choice of standard of care treatment, leukapheresis, etc) was seemingly restricted with no exceptions for specific functions ("Subject level assigned treatment arm and treatment actually received (…) will be restricted to the sponsor"). Furthermore, medical monitors, safety monitors, clinical operations managers were granted access to restricted subject level data.

The DSMB was to review safety data every 6 months from the time the first subject is randomized until the primary EFS analysis. Additionally, the DSMB was to review safety and efficacy data at the time of

the planned interim EFS analysis. The DSMB was tasked to also review SAE information and SUSARs on a regular basis throughout the study.

## *Statistical methods*

*Analysis sets*

The primary analysis of all efficacy endpoints was to be conducted in the FAS, defined as all randomized subjects according to the ITT principle.

The safety analysis set was defined as the subset of all randomized subjects who receive at least one dose of axicabtagene ciloleucel or standard of care chemotherapy and a safety ASCT analysis set was defined as the subset of subjects randomized to the SOCT arm who underwent transplant as part of protocol therapy. Subjects were to be analyzed according to the treatment received.

The primary analysis of HRQoL was to be performed on the subset of subjects in the FAS who have a baseline and at Day 150 post-randomization assessment.

*Primary endpoint*

EFS was defined as the time from randomization to the earliest date of disease progression per Lugano Classification (Cheson et al, 2014), commencement of new lymphoma therapy, or death from any cause. For the primary analysis of EFS, disease progression events and censoring times were determined by blinded central review. Details for the definition of EFS events and timing, and censoring times were defined in the study protocol.

A stratified (randomization stratification factors) log-rank test was to be used for the primary comparison of EFS. Additionally, stratified (randomization stratification factors) Cox regression models were to be used to provide the estimated EFS hazard ratio and 2-sided 95% confidence intervals for axicabtagene ciloleucel relative to SOCT. The median EFS time and event-free rates at 3-month intervals were to be provided.

Sensitivity analyses were to be performed using the actual stratification factor values, in which the strata for relapse ≤ 6 months of first-line therapy and relapse from 6 to 12 months of first-line therapy were determined based on the time of completion of the first-line therapy (rather than time of initiation **or** completion). Further sensitivity analyses of EFS were to be performed to assess ascertainment time bias in disease progression: Progression events that occurred between scheduled assessments were to be moved forward to the next schedule assessment after / before the observed progression, and EFS events that occurred after more than one missed visit were to be censored at the last evaluable disease assessment or visit prior to the observed progression. Additionally, a sensitivity analysis in which subjects in the axicabtagene ciloleucel arm who underwent SCT while in an axicabtagene ciloleucel induced response were to be considered to have had an EFS event on the date of SCT. EFS based on investigator disease assessments was to be analyzed with the same methods as EFS.

*Key secondary endpoints*

ORR was defined as the incidence of either a complete response or a partial response by the Lugano Classification (Cheson et al, 2014) as determined by blinded central review. All subjects who did not meet the criteria for an objective response by the analysis cutoff date were to be considered non-responders. Disease assessments obtained after randomization and up to an observation of progression per Lugano Classification were to be used. Derivation of best response was to include all

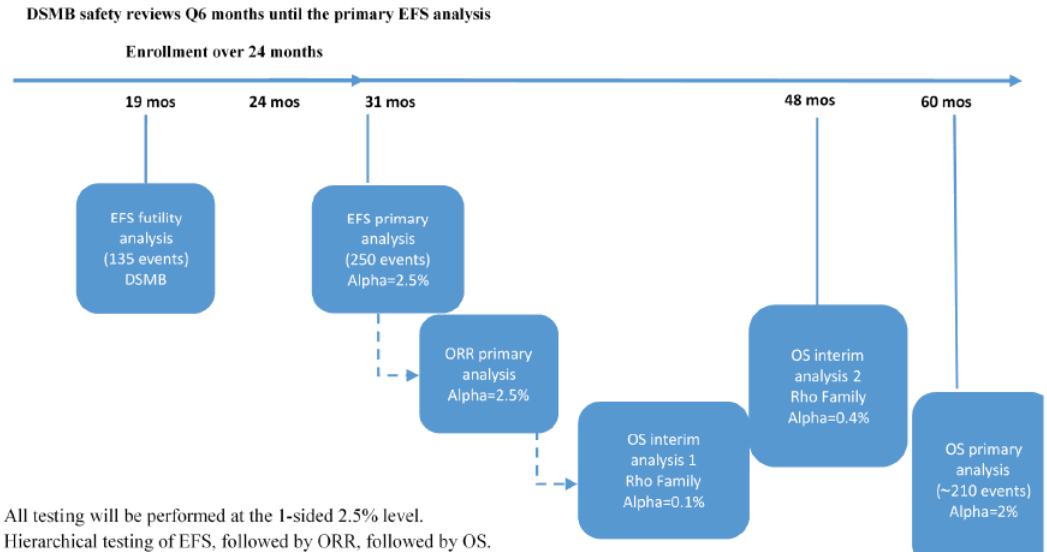
assessments until an EFS event, including any assessments obtained after SCT for the SOCT arm. Testing of ORR was to be performed with a stratified (randomization factor) Cochran-Mantel-Haenszel test for the common odds ratio of response. An exact binomial 2-sided 95% confidence interval was to be generated for the objective response rates and best response rates for each treatment arm. Wilson's score method with continuity correction will be used to calculate 95% confidence intervals for the difference in objective response rates between treatment arms (Newcombe 1998).

OS was defined as the time from randomization to death from any cause. Subjects who have not died by the analysis data cutoff date were to have survival time censored at their last date known to be alive. For subjects alive or dead after the data cutoff date, survival time was to be censored at the data cutoff date. A stratified (randomization stratification factors) log-rank test was to be used for the primary comparison of OS. Additionally, a stratified (randomization factor) Cox regression model was to be used to provide the estimated OS hazard ratio and 2-sided 95% confidence intervals.

*Multiplicity control (over endpoints)*

To preserve the overall significance level, statistical testing of the primary and key secondary efficacy endpoints was to follow a hierarchical scheme (see also Figure 4). EFS was to be tested first at the primary EFS analysis. Conditional on a statistically significant improvement in EFS, ORR was to be tested at the 2.5% level at the time of the primary EFS analysis. Conditional on a statistically significant improvement in EFS and ORR, OS was be tested up to 3 times at an overall 1-sided alpha level of 2.5% (see description of interim analyses below).

**Figure 4. Study Testing Scheme**




All testing will be performed at the 1-sided 2.5% level.
Hierarchical testing of EFS, followed by ORR, followed by OS.
Three analyses of OS are planned; a first interim analysis at the time of the primary EFS analysis, a second interim analysis when approximately 160 deaths have been observed or no later than 5 years after the first subject is randomized, and a primary OS analysis when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized.

*Interim analyses*

One interim analysis of EFS and 2 interim analyses of OS were planned.

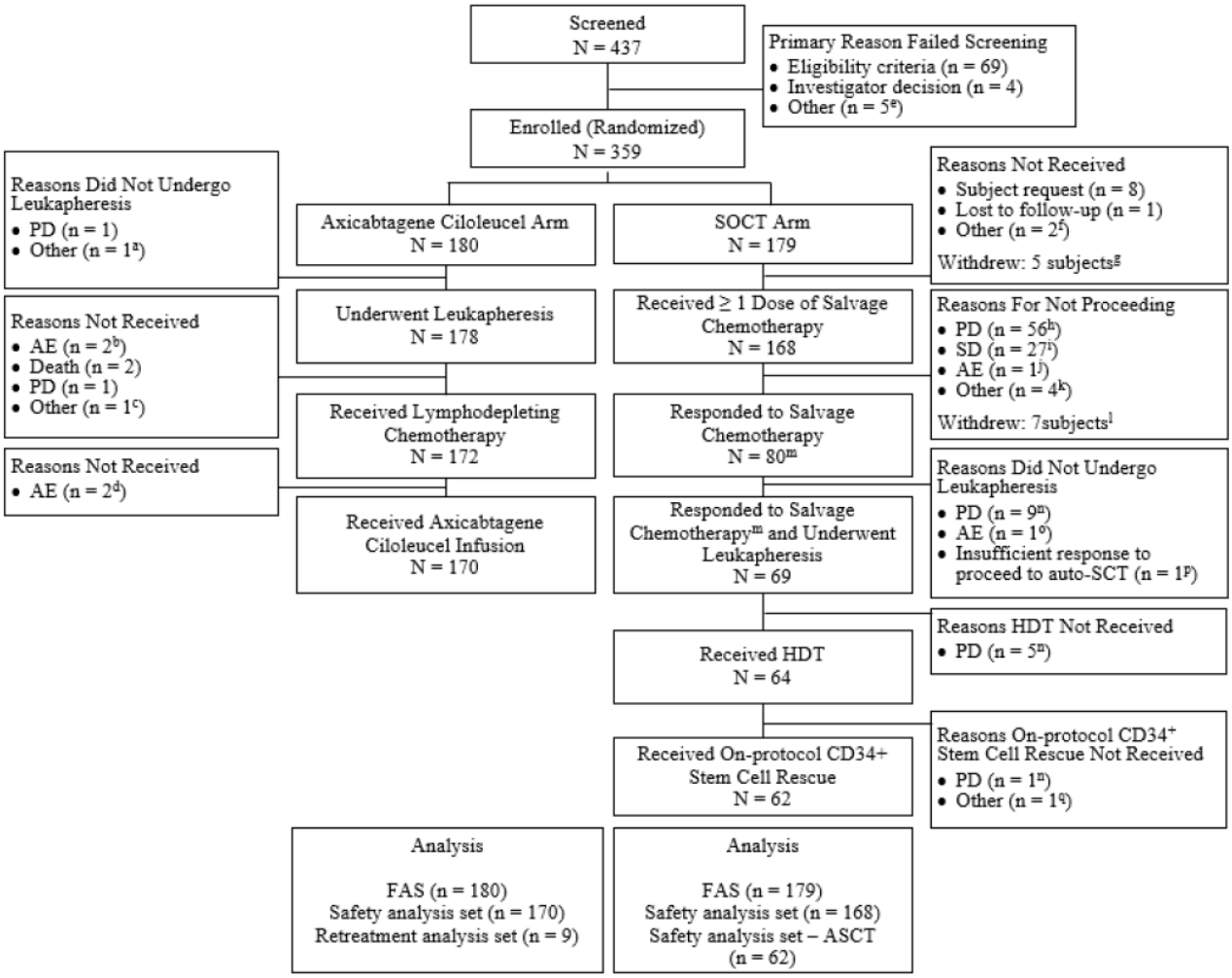
The interim EFS analysis was for futility and was to occur when 135 EFS events had been observed. An O'Brien-Fleming spending function of the Lan-DeMets family was to be used to allocate the type II error between the interim and primary analyses. The futility stopping rule was non-binding. Under the null hypothesis, the probability of stopping for futility at this interim analysis was approximately 60%.

The required 135 EFS events were anticipated to occur approximately 19 months after the first subject was randomized. The primary analysis of EFS was to be conducted when all randomized subjects had had the opportunity to be followed to the Month 9 disease assessment and 250 EFS events as determined by blinded central review had been observed. If more than 250 EFS events were observed at the time of the data cutoff for the primary analysis, all observed events were to be used in the analysis. Prior to the primary efficacy analysis, modeling and monitoring of cumulative EFS events was to be performed to determine a data cutoff date to achieve the planned analysis target event goal.

Conditional upon statistically significant tests of EFS and ORR, testing of OS was to be performed. Two interim analyses of OS were to occur, a first at the time of the primary EFS analysis and a second when approximately 160 deaths had been observed or no later than 4 years after the first subject was randomized. A spending function of the Rho family (Kim & DeMets 1987) with parameter (rho = 6) was to be used to allocate the alpha between the 2 interim analyses of OS and the primary analysis of OS. Approximately 110 OS events were anticipated at the time of the interim OS analysis 1, and 160 at the time of the second OS interim. The primary analysis of OS was to occur when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized. The protocol stated that, based on the alpha spending function and projected event rates, alpha was to be allocated as 0.1% (IA1), 0.4% (IA2), and 2% for the primary analysis of OS. Notably, this is not in line with the defined spending function, which would have led to an allocation of 0.05% (IA1), 0.5% (IA2), and 2.4% (primary analysis).

## *Results*

## Participant flow




Abbreviations: AE, adverse event; ALT, alanine aminotransferase; auto-SCT, autologous stem cell transplant; CVA, cerebrovascular accident; FAS, full analysis set; HDT, high-dose therapy; PD, progressive disease; PET-CT, positron emission tomography – computed tomography; PR, partial response; R-EPOCH, rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisolone; R-DHAP, rituximab plus dexamethasone, cytarabine, and cisplatin; R-GDP, rituximab plus gemcitabine, dexamethasone, and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOCT, standard of care therapy; SD, stable disease; TBI, total body irradiation.
a. Subject was ineligible (Listing 16.1.1.1).
b. One subject had an AE of ALT increased; 1 subject had an AE of hyperbilirubinemia (Listing 16.3.1.1).
c. Subject in false progression at baseline; reassessment showed he was not progressing (Listing 16.1.1.1).
d. One subject had an AE of CVA; 1 subject had an AE of small intestinal perforation (Listing 16.3.1.1).
e. Three subjects because of reasons related to insurance; 1 subject due to rapid progression, and 1 subject opted out. (Listing 16.1.5.1).
f. One subject had a negative disease biopsy; 1 subject had a false positive PET-CT and no refractory DHL after R-EPOCH x 5 (Listing 16.1.1.2).
g. Withdrawals: 5 subjects withdrew with full consent due to subject request (Listing 16.1.1.2). Subjects are also included in the categories of reasons not received.
h. Includes 4 subjects with PD who were leukapheresed (Listing 16.1.1.2). PD represents best response to salvage chemotherapy.
i Includes 1 subject with SD who was leukapheresed (Listing 16.1.1.2 and Listing 16.2.3.2). SD represents best response to salvage chemotherapy.
j. Subject had an AE of acute kidney injury (Listing 16.1.1.2 and Listing 16.3.2.1).

k. Includes 1 subject with lack of response to salvage chemoimmunotherapy with R-ICE; 1 subject who did not tolerate RGDP and switched to R-ICE; 1 subject who changed treatment after 1 cycle of R-DHAP due to renal impairment; and 1 subject with insufficient overall response) to proceed to auto-SCT per investigator (Listing 16.1.1.2).
l. Withdrawals: Subjects withdrew with full consent; 4 subjects completed therapy but no response; 3 subjects with PD (Listing 16.1.1.2). Subjects are also included in the categories of reasons for not proceeding.
m. As determined by the investigator.
n. PD represents disease progression after an initial response to salvage chemotherapy.
o. Subject had an AE of blood stem cell harvest failure (Listing 16.1.1.2 and Listing 16.3.2.1).
p. As determined by the investigator (Listing 16.1.1.2).
q. Subject was inadvertently enrolled on an alternative protocol (Listing 16.1.1.2).

## Recruitment

## Conduct of the study

Study protocol amendments

The original protocol, dated 22 May 2017, was amended 6 times in the US; for all other regions, the protocol was amended 5 times. However, no subjects were treated until Amendment 2 (dated 21 November 2017) and therefore, changes made before and in Amendment 2 are not provided here. Amendment 3 was not submitted to any IRBs or ECs, as well as any ex-US health authorities (HA); therefore, all changes made in Amendment 3 and Amendment 4 were implemented in, and described below under, Amendment 4. Major changes after protocol Amendment 4 and for all subsequent amendments are also summarized below. Amendment 5 was submitted to and approved by HAs, IRBs and ECs outside of the US; no subjects were enrolled under this amendment in the US. Amendment 5.1 was subsequently submitted to and approved by the FDA and IRBs/ECs in the US.

*Amendment 4: 19 March 2019*

- Broadened the definition of the time point from which the period of relapse is determined for the stratification factors from "relapse ≤ 6 months of initiating first-line therapy" and "relapse > 6 and ≤ 12 months of initiating first-line therapy" to "relapse ≤ 6 months of first-line therapy" and "relapse > 6 and ≤ 12 months of first-line therapy," where "of" indicates either from initiation or completion of first-line therapy.
- Broadened the definition of the time point from which progression is determined for the inclusion sub-criterion "partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression" from "≤ 12 months of initiating first-line therapy" to "≤ 12 months of first-line therapy," where "of" indicates either from initiation or completion of first-line therapy.
- Broadened the definition of the time point from which the period of relapse is determined for the inclusion sub-criterion "relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse" from "≤ 12 months of initiating first-line therapy" to "≤ 12 months of firstline- therapy," where "of" indicates either from initiation or completion of first-line therapy.
- Updated the inclusion criteria to maintain alignment with the WHO lymphoid malignancy categories, wherein changes made in 2016 led to the recognition of DLBCL subtypes of T-cell/histiocyte-rich large B-cell lymphoma, EBV+ DLBCL, and primary cutaneous DLBCL, leg type as unique entities and the HGBL category was created {Swerdlow 2016}. Therefore, inclusion criteria were updated from DLBCL including transformation from FL to LBCL including DLBCL, NOS; HGBL with or without MYC and BCL2 and/or BCL6 rearrangement; DLBCL arising from FL; T-cell/histiocyte-rich large B-cell lymphoma; DLBCL associated with chronic inflammation; primary cutaneous DLBCL, leg type; and EBV+ DLBCL.

- Clarified the required duration of subject observation after axicabtagene ciloleucel infusion was to be aligned with country-specific requirements.
- Aligned requirements for initiating leukapheresis, lymphodepleting chemotherapy, axicabtagene ciloleucel infusion and retreatment with the axicabtagene ciloleucel clinical study program.
- Clarified the duration of the period for collecting information for concomitant therapy was to include targeted concomitant therapies from Study Day 150 until Month 12, and that recording of this information stopped at Month 12, change in lymphoma therapy, or disease progression, whichever came first.
- Updated that PET-CTs were to continue through Month 9 or until a change in lymphoma therapy or disease progression, whichever came first. Clarified that imaging follow-up was to be performed for subjects who discontinued protocol therapy due to an assessment of PD, but for whom there was no change in lymphoma therapy. Clarified that subjects for whom CT scans with contrast were contraindicated were to undergo MRI with contrast in addition to noncontrast CT scans.
- Clarified that samples of apheresis and final product were to be retained and tested to understand the mechanism of action and safety profile of axicabtagene ciloleucel.
- Updated the SOA tables (for both treatment arms) to include respiratory rate as a vital sign procedure and the WPAI:GH was added to the Therapy days –5 and 0 assessments to align with collection of the other PROs. The axicabtagene ciloleucel treatment arm SOA was updated with an additional blood draw for PBMCs at Treatment day 3 and the mini-mental state examination was removed as a mandatory part of the neurologic assessment. The SOCT arm SOA table was updated with additional blood draws at Cycle 1 and Study Days 50, 100, and 150 and for long-term follow-up assessments at Months 9, 12, 18, 24, 36, 48, and 60.
- Added 3 timepoints for PRO assessment (Months 18, 21, and 24) to the long-term follow-up
- Updated the AE reporting period to post-randomization through Study Day 150 or a change in lymphoma therapy, whichever occurred first
- Updated the SAE reporting period to after signing of the informed consent through the Study Day 150 visit or until initiation of a new lymphoma therapy, whichever occurred first. The reporting period for targeted SAEs was updated to 5 years for the SOCT arm and 15 years for the axicabtagene ciloleucel arm, or until disease progression, whichever occurred first.
- Described the reporting requirements for deaths to match the current axicabtagene ciloleucel clinical study program

*Amendment 5 (current protocol version for ex-US HAs and IRBs/ECs): 25 June 2020*

- Modified the primary EFS analysis event trigger from 270 to approximately 250 EFS events with an acceptable lower limit for the observed total EFS events of 225, which was to maintain the power for the primary analysis to within 5% of the targeted 90%.
- Increased the required duration of follow-up for the primary analysis of EFS from the Study Day 150 assessment to the Month 9 assessment
- Added a second interim OS analysis and a sensitivity analyses of OS. The second interim analysis of OS was to occur when approximately 160 deaths have been observed or no later than 4 years after the first subject is randomized. The sensitivity analyses were added to address the confounding effect from treatment switching.
- Added a time frame for the primary analysis of OS so that it was to occur either when approximately 210 deaths have been observed or no later than 5 years after the first subject was randomized.

- Added TTNT as an exploratory endpoint
- Provided guidance for sites to encourage collection of a biopsy confirming disease progression and to submit the biopsied tissue to the central laboratory
- Updated the revised pregnancy and lactation reporting language to be consistent with EU requirements and to align across Kite programs
- Clarified the TEAE definition as any AE that begins on or after the first dose study treatment (axicabtagene ciloleucel infusion or standard of care salvage chemotherapy), to be in alignment with the definition used in other Kite studies.

*Amendment 5.1 (US only): 16 September 2020*

- Reference to an acceptable lower limit for the observed total EFS events to trigger the primary analysis was removed at the request of the FDA
- Removed "approximately" from the 250 events required to trigger the primary analysis at the request of the FDA

Changes in Planned Analyses

The following changes in analyses or additional analyses occurred after SAP finalization:

- The primary EFS analysis was planned to occur after 250 EFS events had been observed in the study. Because the time to reach 250 EFS events was longer than estimated, the first interim OS analysis was conducted at 153 events instead of the planned 110 events. As a result, the interim OS analysis conducted at 153 events meets the criteria for both originally planned interim OS analyses at 110 and 160 events. The only subsequent planned OS analysis will be the primary (final) OS analysis, expected to occur when 210 events are observed or no later than 5 years after the first subject is randomized.
- PFS based on central assessment was analyzed with the same methods per investigator assessment, as well as in subgroups defined by the baseline characteristics in Section 7.7.10.2. and presented in data tables.
- Modifications within some categories of baseline characteristics and subgroup covariates occurred.
- HDT-related TEAEs (for the SOCT arm) are provided in data tables in addition to the SAP-specified salvage chemotherapy-related and auto-SCT-related TEAE tables.

The following clarifications to definitions were made after SAP finalization:

- Concordance between EFS determined by central and investigator assessment was determined using EFS events instead of progression events.
- Therapy day 0 is used in select data tables and listings in the following instances:
    - When referring to the day of administration of the first dose of salvage chemotherapy in the SOCT arm
    - In tables, listings, and narratives that use one term to refer to the day of administration of the first dose of either axicabtagene ciloleucel in the axicabtagene ciloleucel arm or salvage chemotherapy in the SOCT arm.

- The definition of the QoL analysis set in the data tables was aligned with the definition provided in the Supplemental PRO SAP as subjects who had a baseline and at least 1 completed post-randomization measurement through the Study Day 150 visit

The definition of bone marrow failure was aligned with the axicabtagene ciloleucel Investigator's Brochure and is therefore not identified as a potential risk of axicabtagene ciloleucel

## Baseline data

### Demographics

Subject demographics were generally comparable between the 2 treatment arms. The median age was 59 years (range: 21 to 81 years), and 109 subjects (30%) were ≥ 65 years of age. The majority of subjects were male (237 subjects, 66%) and White (297 subjects, 83%). Most subjects were randomized in North America (270 subjects, 75%), of whom the majority were in the US (250 subjects, 70%). Of the subjects randomized in Europe (79 subjects, 22%), most subjects were in the Netherlands (25 subjects, 7%).
Treatment arms were generally well-balanced, but a difference of ≥ 10% was observed between the axicabtagene ciloleucel and SOCT arms for sex (male: 61% versus 71%, respectively).

**Table 2. Demographics (FAS)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) | Overall (N = 359) |
|---|---|---|---|
| Age (years) | | | |
| n | 180 | 179 | 359 |
| Mean (STDEV) | 57.1 (12.0) | 57.4 (12.2) | 57.2 (12.1) |
| Median (Q1, Q3) | 58.0 (52.0, 66.0) | 60.0 (49.0, 67.0) | 59.0 (51.0, 67.0) |
| Min, Max | 21, 80 | 26, 81 | 21, 81 |
| Age category, n (%) | | | |
| < 65 years | 129 (72) | 121 (68) | 250 (70) |
| ≥ 65 years | 51 (28) | 58 (32) | 109 (30) |
| Sex, n (%) | | | |
| Male | 110 (61) | 127 (71) | 237 (66) |
| Female | 70 (39) | 52 (29) | 122 (34) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 10 (6) | 8 (4) | 18 (5) |
| Not Hispanic or Latino | 167 (93) | 169 (94) | 336 (94) |
| Not Reported | 3 (2) | 2 (1) | 5 (1) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 0 (0) | 1 (1) | 1 (0) |
| Asian | 12 (7) | 10 (6) | 22 (6) |
| Black or African American | 11 (6) | 7 (4) | 18 (5) |
| Native Hawaiian or Other Pacific Islander | 2 (1) | 1 (1) | 3 (1) |
| White | 145 (81) | 152 (85) | 297 (83) |
| Other | 10 (6) | 8 (4) | 18 (5) |
| Country, n (%) | | | |
| United States | 130 (72) | 120 (67) | 250 (70) |
| Netherlands | 11 (6) | 14 (8) | 25 (7) |
| Canada | 10 (6) | 10 (6) | 20 (6) |
| Spain | 6 (3) | 9 (5) | 15 (4) |
| United Kingdom | 4 (2) | 8 (4) | 12 (3) |
| Belgium | 4 (2) | 3 (2) | 7 (2) |
| France | 4 (2) | 2 (1) | 6 (2) |
| Germany | 1 (1) | 5 (3) | 6 (2) |
| Israel | 4 (2) | 2 (1) | 6 (2) |
| Australia | 2 (1) | 2 (1) | 4 (1) |
| Austria | 1 (1) | 2 (1) | 3 (1) |
| Italy | 2 (1) | 1 (1) | 3 (1) |
| Sweden | 0 (0) | 1 (1) | 1 (0) |
| Switzerland | 1 (1) | 0 (0) | 1 (0) |
| Region, n (%) | | | |
| North America | 140 (78) | 130 (73) | 270 (75) |
| Europe | 34 (19) | 45 (25) | 79 (22) |
| Israel | 4 (2) | 2 (1) | 6 (2) |
| Australia | 2 (1) | 2 (1) | 4 (1) |

Data cutoff date = 18MAR2021.
Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
Source: Table 14.1.3.1.

## Baseline and disease characteristics

Overall, baseline characteristics were generally comparable between the 2 treatment arms. As categorized by the investigator, the most common disease type for subjects in both the axicabtagene ciloleucel and SOCT arms were DLBCL, NOS (110 of 180 subjects [61%] and 116 of 179 subjects [65%], respectively), HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement (43 subjects [24%] and 27 subjects [15%], respectively), and large cell transformation from FL (19 subjects [11%] and 27 subjects [15%], respectively). Forty-four subjects (24%) in the axicabtagene ciloleucel arm and 35 subjects (20%) in the SOCT arm had double-expressor lymphoma as reported by the investigator.

Disease subtypes were defined differently by the central laboratory than by the investigator; DLBCL NOS was considered a diagnosis of exclusion per the central laboratory; cases of incomplete evaluation (eg, inadequate samples or sample types, or lack of clinical history such as the location of the tumor) were considered by the central laboratory to be DLBCL without further classification of subtype possible. Subjects in the axicabtagene ciloleucel and SOCT arms were categorized as DLBCL NOS/without further classification possible (126 subjects [70%] and 120 subjects [67%], respectively); HGBL with *MYC*, *BCL2*, and/or *BCL6* rearrangements (31 subjects [17%] and 25 subjects [14%], respectively) or HGBL, NOS, (1 subject [1%] in the SOCT arm); the remaining subjects were categorized under not confirmed, missing, or other.

Per the randomization stratification factor of response to first-line therapy as collected in the IxRS, the majority of subjects had primary refractory disease (133 subjects [74%] and 131 [73%] in the axicabtagene ciloleucel and SOCT arms, respectively). Similar percentages of subjects with primary refractory disease were derived from the clinical database (133 subjects [74%] and 132 subjects [74%] in the axicabtagene ciloleucel and SOCT arms, respectively) but the percentages of subjects whose disease relapsed ≤ 6 months or > 6 to ≤ 12 months of first-line therapy differed between the IxRS and the derived data due to a protocol change that broadened the definition of the time point from which the period of relapse is determined.

Per the randomization stratification factor of sAAIPI score as collected in the IxRS, approximately half of subjects had an sAAIPI score of 0 or 1 (98 subjects [54%] and 100 subjects [56%] in the axicabtagene ciloleucel and SOCT arms, respectively). The percentage of subjects with sAAIPI scores of 0 or 1 were similar when derived from the clinical database (94 subjects [52%] and 100 subjects [56%] in the axicabtagene ciloleucel and SOCT arms, respectively). In the axicabtagene ciloleucel and SOCT arms, the relevant components of sAAIPI were elevated LDH levels (101 subjects [56%] and 94 subjects [53%], respectively), stage III/IV disease (139 subjects [74%] and 146 subjects [82%], respectively), and ECOG performance status > 1 (which did not apply to any subjects as, per protocol inclusion criteria, all subjects

(100%) had an ECOG score of 0 or 1).

In addition, 62% of subjects had extranodal disease, with some variability (≥ 10% differences) observed between the axicabtagene ciloleucel and SOCT arms (57% versus 67%, respectively).

**Table 3. Baseline characteristics**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) | Overall (N = 359) |
|---|---|---|---|
| ECOG performance status, n (%) | | | |
| 0 | 95 (53) | 100 (56) | 195 (54) |
| 1 | 85 (47) | 79 (44) | 164 (46) |
| Best response to first-line therapy, n (%) | | | |
| Complete response | 46 (26) | 47 (26) | 93 (26) |
| Partial response | 60 (33) | 62 (35) | 122 (34) |
| Stable disease | 11 (6) | 11 (6) | 22 (6) |
| Progressive disease | 63 (35) | 59 (33) | 122 (34) |
| Response to first-line therapy at randomization (IxRS), n (%) | | | |
| Primary refractory | 133 (74) | 131 (73) | 264 (74) |
| Relapse ≤ 6 months of first-line therapy[a] | 9 (5) | 9 (5) | 18 (5) |
| Relapse > 6 and ≤ 12 months of first-line therapy[a] | 38 (21) | 39 (22) | 77 (21) |
| Second-line age-adjusted International Prognostic Index total score (IxRS), n (%) | | | |
| 0 - 1 | 98 (54) | 100 (56) | 198 (55) |
| 2 - 3 | 82 (46) | 79 (44) | 161 (45) |
| Derived response to first-line therapy at randomization, n (%) | | | |
| Primary refractory | 133 (74) | 132 (74) | 265 (74) |
| Relapse ≤ 6 months of the completion of the first-line therapy[a] | 26 (14) | 22 (12) | 48 (13) |
| Relapse > 6 and ≤ 12 months of the completion of the first-line therapy[a] | 20 (11) | 24 (13) | 44 (12) |
| Missing | 1 (1) | 1 (1) | 2 (1) |
| Derived second-line age-adjusted International Prognostic Index total score, n (%) | | | |
| 0 | 26 (14) | 18 (10) | 44 (12) |
| 1 | 68 (38) | 82 (46) | 150 (42) |

| | | | |
|---|---|---|---|
| 2 | 86 (48) | 79 (44) | 165 (46) |
| 0 or 1 | 94 (52) | 100 (56) | 194 (54) |
| 2 or 3 | 86 (48) | 79 (44) | 165 (46) |
| Second-line age-adjusted International Prognostic Index (investigator), n (%) | | | |
| ECOG performance status > 1 | 0 (0) | 0 (0) | 0 (0) |
| Stage III/IV | 139 (77) | 146 (82) | 285 (79) |
| Elevated LDH (LDH > ULN per local laboratory reference range) | 101 (56) | 94 (53) | 195 (54) |
| Disease type per investigator, n (%) | | | |
| DLBCL, NOS | 110 (61) | 116 (65) | 226 (63) |
| T cell/histiocyte rich LBCL | 5 (3) | 6 (3) | 11 (3) |
| Epstein-Barr virus (EBV) + DLBCL | 2 (1) | 0 (0) | 2 (1) |
| Large cell transformation from follicular lymphoma | 19 (11) | 27 (15) | 46 (13) |
| HGBL with or without MYC and BCL2 and/or BCL6 rearrangement | 43 (24) | 27 (15) | 70 (19) |
| Primary cutaneous DLBCL (leg type) | 1 (1) | 0 (0) | 1 (0) |
| Other | 0 (0) | 3 (2) | 3 (1) |
| Molecular subgroup per investigator, n (%) | | | |
| GCB-like | 96 (53) | 84 (47) | 180 (50) |
| Non-GCB like | 47 (26) | 54 (30) | 101 (28) |
| Not tested | 37 (21) | 41 (23) | 78 (22) |
| Double expressor lymphoma as determined per investigator, n (%) | | | |
| Yes | 44 (24) | 35 (20) | 79 (22) |
| No | 85 (47) | 93 (52) | 178 (50) |
| Not tested | 51 (28) | 51 (28) | 102 (28) |
| Double/triple hit status per investigator, n (%) | | | |
| HGBL - double hit | 30 (17) | 18 (10) | 48 (13) |
| HGBL - triple hit | 10 (6) | 16 (9) | 26 (7) |
| Negative | 110 (61) | 102 (57) | 212 (59) |
| Not tested | 30 (17) | 43 (24) | 73 (20) |
| Disease stage, n (%) | | | |
| I | 10 (6) | 6 (3) | 16 (4) |

| | | | |
|---|---|---|---|
| II | 31 (17) | 27 (15) | 58 (16) |
| III | 35 (19) | 33 (18) | 68 (19) |
| IV | 104 (58) | 113 (63) | 217 (60) |
| Molecular subgroup per central laboratory, n (%)[b] | | | |
| GCB-like | 109 (61) | 99 (55) | 208 (58) |
| ABC-like | 16 (9) | 9 (5) | 25 (7) |
| Unclassified | 17 (9) | 14 (8) | 31 (9) |
| Not applicable | 10 (6) | 16 (9) | 26 (7) |
| Missing | 28 (16) | 41 (23) | 69 (19) |
| Disease type per central laboratory, n (%) | | | |
| DLBCL NOS/without further classification possible[c] | 126 (70) | 120 (67) | 246 (69) |
| HGBLymphoma, NOS | 0 (0) | 1 (1) | 1 (0) |
| HGBLymphoma, with MYC/BCL2/BCL6 Rearrangements | 31 (17) | 25 (14) | 56 (16) |
| Not Confirmed | 15 (8) | 13 (7) | 28 (8) |
| Other | 5 (3) | 5 (3) | 10 (3) |
| Missing | 3 (2) | 15 (8) | 18 (5) |
| Prognostic marker per central laboratory, n (%) | | | |
| HGBL - double hit | 25 (14) | 15 (8) | 40 (11) |
| HGBL - triple hit | 6 (3) | 10 (6) | 16 (4) |
| Double expressor lymphoma | 57 (32) | 62 (35) | 119 (33) |
| MYC rearrangement | 15 (8) | 7 (4) | 22 (6) |
| NA[d] | 74 (41) | 70 (39) | 144 (40) |
| Missing | 3 (2) | 15 (8) | 18 (5) |
| CD19 IHC positive by central laboratory at baseline, n (%)[e] | | | |
| Yes | 144 (80) | 134 (75) | 278 (77) |
| No | 13 (7) | 12 (7) | 25 (7) |
| Missing | 23 (13) | 33 (18) | 56 (16) |
| CD19 H-Score, n (%) | | | |
| ≤ 150 | 85 (47) | 67 (37) | 152 (42) |
| > 150 | 72 (40) | 79 (44) | 151 (42) |
| Missing[f] | 23 (13) | 33 (18) | 56 (16) |

| | | | |
|---|---|---|---|
| Presence of B symptoms, n (%) | | | |
| Yes | 21 (12) | 29 (16) | 50 (14) |
| No | 159 (88) | 150 (84) | 309 (86) |
| S (Splenic involvement), n (%) | | | |
| Yes | 19 (11) | 33 (18) | 52 (14) |
| No | 161 (89) | 146 (82) | 307 (86) |
| E (Extranodal disease), n (%) | | | |
| Yes | 103 (57) | 120 (67) | 223 (62) |
| No | 77 (43) | 59 (33) | 136 (38) |
| X (Bulky disease), n (%) | | | |
| Yes | 13 (7) | 16 (9) | 29 (8) |
| No | 167 (93) | 163 (91) | 330 (92) |
| Bone marrow involvement[g], n (%) | | | |
| Yes | 17 (9) | 15 (8) | 32 (9) |
| No | 163 (91) | 164 (92) | 327 (91) |
| Screening bone marrow assessment[h], n (%) | | | |
| Lymphoma present | 17 (9) | 14 (8) | 31 (9) |
| If PET/CT, result | | | |
| Focal involvement | 5 (3) | 9 (5) | 14 (4) |
| Diffuse involvement | 8 (4) | 1 (1) | 9 (3) |
| Lymphoma not present | 161 (89) | 164 (92) | 325 (91) |
| If PET/CT, result | | | |
| Negative | 126 (70) | 127 (71) | 253 (70) |
| Focal involvement[i] | 1 (1) | 0 (0) | 1 (0) |
| Diffuse involvement[i] | 1 (1) | 0 (0) | 1 (0) |
| Indeterminate | 0 (0) | 1 (1) | 1 (0) |
| If PET/CT, result | | | |
| Bone marrow not evaluable | 0 (0) | 1 (1) | 1 (0) |
| Number of prior lines of therapy, n (%) | | | |
| 1 | 180 (100) | 179 (100) | 359 (100) |

Data cutoff date = 18MAR2021.
Abbreviations: ABC, activated B-cell; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; HGBL, high-grade B-cell lymphoma; IHC, immunohistochemistry; IxRS, interactive voice/web response system; LDH, lactate dehydrogenase; Max, maximum; Min, minimum; NA, not applicable; NOS, not otherwise

specified; PET/CT, positron emission tomography-computed tomography; Q1, first quartile; Q3, third quartile; STDEV, standard deviation; ULN, upper limit of normal.
Notes: One subject did not perform screening bone marrow assessment; another subject's screening bone marrow assessment was not evaluable. One subject signed the wrong informed consent form and then signed the correct one after randomization. HGBL – double hit is defined as presence of *MYC* and either *BCL-2* or *BCL6* rearrangements; HGBL - triple hit is defined as presence of *BCL-2*, *BCL6*, and *MYC* rearrangements; double-expressor lymphoma is defined as overexpression of *MYC* and *BCL-2* proteins not related to underlying chromosomal rearrangements.

a For data collected in the IxRS, relapse after first-line therapy was assessed for subjects enrolled until Amendment 4 using ≤ 6 months from initiation of first-line therapy and using ≤ 6 months of first-line therapy for subjects enrolled after Amendment 4; this also applies for relapse > 6 months ≤ 12 months (refer to Section 7.8.1). Data derived from the clinical database assessed relapse after first-line therapy using ≤ 6 months of completion of first-line therapy.

b Missing records of molecular subgroup per central laboratory are due to insufficient tissue or biopsy not available at central laboratory. NA in the molecular subgroup per central laboratory category indicates the sample failed to meet quality control.

c Disease type was considered to be DLBCL, NOS, when all other disease subtypes could be excluded by laboratory analyses; cases of incomplete evaluation (eg, inadequate samples or sample types or lack of clinical history such as the location of the tumor) were considered by the central laboratory to be DLBCL without further classification of subtype possible. Per the central laboratory, DLBCL NOS = 32 subjects (18%) and 26 subjects (15%) in the axicabtagene ciloleucel and SOCT arms, respectively; and DLBCL without further classification possible = 94 subjects (52%) and 94 subjects (53%), respectively.

d Disease types (per central laboratory) of DLBCL, NOS; HGBL, NOS; other; and not confirmed are assigned "NA" in prognostic marker per central laboratory.

e CD19 IHC positive is defined as the H-score of staining greater than or equal to 5.

f Missing CD19 H-scores are mainly due to quantity not sufficient, biopsy not available at central laboratory, CD19 negative, or tumor tissue not present in sample.

g Bone marrow involvement is collected on the diagnosis history case report form.

h Screening bone marrow assessment is done by aspirate and biopsy or PET/CT.

i In these cases, reports of focal or diffuse involvement indicates fluorodeoxglucose uptake but may not indicate lymphoma involvement per investigator discretion.

Source: Modified from Table 14.1.4.1.

Baseline characteristics and prior therapies for the FAS were generally similar to those for the safety analysis set. Baseline characteristics for subjects who received auto-SCT in the SOCT arm were generally similar to those for subjects in the SOCT arm in the FAS, except that more subjects had CR in response to first-line therapy (23 subjects [37%] and 47 subjects [26%], respectively), an ECOG score of 0 (42 subjects [68%] and 100 subjects [56%], respectively), and response to first line therapy at randomization of relapse < 6 months and ≤ 12 months of first-line therapy as derived from the clinical database (16 subjects [26%]
and 24 subjects [13%], respectively) and conversely, fewer subjects had primary refractory disease (63% and 74%, respectively).

## Numbers analysed

A total of 359 subjects were randomly assigned in a 1:1 ratio to receive axicabtagene ciloleucel or SOCT, with 180 subjects in the axicabtagene ciloleucel arm and 179 subjects in the SOCT arm.

**Table 4. Analysis Sets (All Randomized Subjects)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) | Overall (N = 359) |
|---|---|---|---|
| Full analysis set, n (%) | 180 (100) | 179 (100) | 359 (100) |
| Safety analysis set, n (%) | 170 (94) | 168 (94) | 338 (94) |
| Safety analysis set – auto-SCT, n (%) | NA | 62 (35) | 62 (17) |
| QoL analysis set, n (%) | 165 (92) | 131 (73) | 296 (82) |
| Retreatment analysis set, n (%) | 9 (5) | NA | 9 (3) |

Data cutoff date = 18MAR2021.
Abbreviations: NA, not applicable; QoL, quality of life; SCT, stem cell transplant.
Notes: 437 subjects were screened. The full analysis set consists of all randomized subjects and subjects are analyzed based on randomized treatment arm. The safety analysis set is defined as the subset of all randomized subjects who receive at least 1 dose of axicabtagene ciloleucel as protocol therapy or standard of care salvage chemotherapy as protocol therapy, and subjects are analyzed by the protocol therapy they received. The safety analysis set – auto-SCT is defined as the subset of subjects who are randomized to the standard of care therapy arm and undergo auto-SCT as part of protocol therapy. The QoL analysis set is defined as the subset of subjects in the full analysis set who have a baseline and any post-baseline assessment up to Day 150 post-randomization QoL assessment. The safety retreatment analysis set consists of subjects in the axicabtagene ciloleucel arm who undergo retreatment with axicabtagene ciloleucel.

The first subject was enrolled (ie, randomized) into ZUMA-7 on 25 January 2018 and enrollment was completed on 04 October 2019; ZUMA-7 is currently ongoing. The data cutoff date for the primary analysis described in this clinical overview was 18 March 2021.

All randomized subjects had the opportunity to be followed for at least 15 months after randomization. The median potential follow-up time (from randomization to the data cutoff date) was 24.94 months (range: 17.48 to 37.75 months). For the 180 subjects in the axicabtagene ciloleucel arm and the 179 subjects in the SOCT arm, the median potential follow-up time was 25.00 months (range: 17.48 to 37.75 months) and 24.84 months (range: 17.58 to 37.26 months), respectively; and the median actual follow-up time was 20.07 months (range: 0.59 to 37.75 months) and 18.23 months (range: 0.03 to 37.26 months), respectively.

**Table 5. Disposition of subjects (FAS)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) | Overall (N = 359) |
|---|---|---|---|
| Subjects randomized, n | 180 | 179 | 359 |
| Axicabtagene ciloleucel | | | |
| Underwent leukapheresis, n (%) | 178 (99) | NA | NA |
| Received bridging therapy, n (%) | 65 (36) | NA | NA |
| Received conditioning chemotherapy, n (%) | 172 (96) | NA | NA |
| Received axicabtagene ciloleucel, n (%) | 170 (94) | NA | NA |

| | | | |
|---|---|---|---|
| Received retreatment axicabtagene ciloleucel, n (%) | 9 (5) | NA | NA |
| Standard of care therapy | | | |
| Received standard of care salvage chemotherapy, n (%) | NA | 168 (94) | NA |
| Underwent leukapheresis of CD34+ stem cells, n (%) | NA | 74 (41) | NA |
| Received high dose therapy, n (%) | NA | 64 (36) | NA |
| Received CD34+ stem cell rescue, n (%) | NA | 62 (35) | NA |
| Subjects who did not receive conditioning chemotherapy, axicabtagene ciloleucel, or standard of care therapy, by reasons, n (%) | 8 (4) | 11 (6) | 19 (5) |
| Adverse event | 2 (1) | 0 (0) | 2 (1) |
| Death | 2 (1) | 0 (0) | 2 (1) |
| Disease progression | 2 (1) | 0 (0) | 2 (1) |
| Subject request | 0 (0) | 8 (4) | 8 (2) |
| Lost to follow-up | 0 (0) | 1 (1) | 1 (0) |
| Other | 2 (1) | 2 (1) | 4 (1) |
| Subjects who received conditioning chemotherapy but not axicabtagene ciloleucel by reasons, n (%) | 2 (1) | NA | NA |
| Adverse event | 2 (1) | NA | NA |
| Subjects who received axicabtagene ciloleucel or standard of care therapy, n (%) | 170 (94) | 168 (94) | 338 (94) |
| Subjects who received bridging therapy, n (%) | 60 (33) | NA | NA |
| Subjects who completed treatment, n (%) | 170 (94) | 89 (50)[a] | 259 (72) |
| Subjects who initiated but did not complete axicabtagene ciloleucel infusion or standard of care by reasons, n (%) | 0 (0) | 79 (44) | 79 (22) |
| Adverse event | 0 (0) | 2 (1) | 2 (1) |
| Disease progression | 0 (0) | 71 (40) | 71 (20) |
| Other | 0 (0) | 6 (3) | 6 (2) |
| Primary reason for ending the study | | | |
| Subjects who did not receive axicabtagene ciloleucel or standard of care therapy, n (%) | 8 (4) | 7 (4) | 15 (4) |
| Death | 8 (4) | 1 (1) | 9 (3) |
| Lost to follow-up | 0 (0) | 1 (1) | 1 (0) |
| Full consent withdrawn | 0 (0) | 5 (3) | 5 (1) |

| | | | |
|---|---|---|---|
| Subjects who received axicabtagene ciloleucel or standard of care therapy, n (%) | 66 (37) | 86 (48) | 152 (42) |
| Death | 64 (36) | 75 (42) | 139 (39) |
| Due to COVID-19 | 4 (2) | 2 (1) | 6 (2) |
| Lost to follow-up | 2 (1) | 2 (1) | 4 (1) |
| Full consent withdrawn | 0 (0) | 7 (4) | 7 (2) |
| Investigator decision | 0 (0) | 1 (1) | 1 (0) |
| Other | 0 (0) | 1 (1) | 1 (0) |
| Follow-up time for all randomized subjects | | | |
| Actual follow-up time (months)[b] | | | |
| n | 180 | 179 | 359 |
| Mean (STDEV) | 19.280 (8.865) | 16.556 (9.474) | 17.922 (9.262) |
| Median (Q1, Q3) | 20.074 (12.649, 25.610) | 18.234 (7.721, 24.411) | 19.154 (9.823, 25.101) |
| Min, Max | 0.59, 37.75 | 0.03, 37.26 | 0.03, 37.75 |
| Potential follow-up time (months)[c] | | | |
| n | 180 | 179 | 359 |
| Mean (STDEV) | 25.198 (5.144) | 25.174 (4.868) | 25.186 (5.002) |
| Median (Q1, Q3) | 25.002 (20.682, 29.207) | 24.838 (21.158, 28.616) | 24.936 (20.961, 28.747) |
| Min, Max | 17.48, 37.75 | 17.58, 37.26 | 17.48, 37.75 |
| Subjects with ≥ 15 months potential follow-up[c], n (%) | 180 (100) | 179 (100) | 359 (100) |

Data cutoff date = 18MAR2021.
Abbreviations: COVID-19, coronavirus disease 2019; eCRF, electronic case report form; Max, maximum; Min, minimum; NA, not applicable; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
Note: In the SOCT arm, subjects who completed treatment are those who completed salvage chemotherapy (2 or 3 cycles), high dose therapy, and stem cell transplant, or those who completed salvage chemotherapy and were assessed as stable disease at Study Day 50 without proceeding to stem cell transplant.
a For 2 subjects, the Study Day 50 disease assessments were updated by the clinical site to SD but the corresponding end of treatment eCRF was not updated (Table 14.1.2.1).
b Actual follow-up time is calculated as (death date or last date known alive – randomization date + 1)/30.4375.
c Potential follow-up time is calculated as (the cutoff date – randomization date + 1)/30.4375.
Source: Table 14.1.2.

## Outcomes and estimation

### Primary Efficacy Endpoint: EFS per Central Assessment

The primary efficacy endpoint was EFS using blinded central assessment. To test the superiority of axicabtagene ciloleucel over SOCT, a log-rank test stratified by randomization factors (response to first-line therapy and sAAIPI) was conducted.

At the time of the data cutoff (18 March 2021), 252 EFS events by blinded central assessment had occurred for 108 subjects (60%) in the axicabtagene ciloleucel arm and 144 subjects (80%) in the SOCT arm.

Axicabtagene ciloleucel treatment was superior to SOCT, with a stratified HR of 0.398 (95% CI: 0.308, 0.514; stratified log-rank $p < 0.0001$). The KM median EFS time for the axicabtagene ciloleucel and SOCT arms was 8.3 months (95% CI: 4.5, 15.8 months; range: 0 to 31 months with censoring [+]) and 2.0 months (95% CI: 1.6, 2.8 months; range: 0 [+] to 33 [+] months), respectively.

The KM estimates of the percentage of subjects who remained event-free at 12 and 24 months after randomization in the axicabtagene ciloleucel arm were 47.2% (95% CI: 39.8%, 54.3%) and 40.5% (95% CI: 33.2%, 47.7%), respectively, compared with 17.6% (95% CI: 12.3%, 23.6%) and 16.3% (95% CI: 11.1%, 22.2%), respectively, in the SOCT arm.

The median follow-up time for EFS using the reverse KM method was 23.0 months (95% CI: 20.9 to 24.0 months) in the axicabtagene ciloleucel arm and 21.2 months (95% CI: 20.4 to 23.7 months) in the SOCT arm.

The primary analysis of EFS used the stratification factors as collected via IxRS at randomization. Sensitivity analyses of EFS using stratification factors derived from the eCRF and EFS without stratification also demonstrated axicabtagene ciloleucel superiority (HR: 0.406, 95% CI: 0.313, 0.525, log-rank p < 0.0001; HR: 0.423, 95% CI: 0.328, 0.544, log-rank p < 0.0001, respectively).

The most common EFS events in either the axicabtagene ciloleucel or SOCT arm were disease progression (82 subjects [46%] and 75 subjects [42%], respectively), new lymphoma therapy (9 subjects [5%] and 63 subjects [35%], respectively), and death from any cause (11 subjects [6%] and 6 subjects [3%], respectively).

At the data cutoff date, 72 subjects (40%) in the axicabtagene ciloleucel arm and 35 subjects (20%) in the SOCT arm were censored, with the most common reason being ongoing response (72 subjects [40%] and 28 subjects [16%], respectively). Of note, only 8 subjects (all in the SOCT arm) of the 359 subjects in the FAS were censored before Month 12.

Twelve subjects (2 in the axicabtagene ciloleucel arm and 10 in the SOCT arm) initiated a new lymphoma therapy in the absence of an evaluable postbaseline disease assessment and had EFS event dates imputed as the randomization date as predefined in the statistical analysis plan.

No subjects in the axicabtagene-ciloleucel arm underwent auto-SCT while in response.

**Table 6. EFS per Blinded Central Assessment (Full Analysis Set)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Number of subjects | 180 | 179 |
| Events, n (%) | 108 (60) | 144 (80) |
| Censored[a], n (%) | 72 (40) | 35 (20) |
| Stratified log-rank p-value | <.0001 | NA |
| Hazard ratio (95% CI), stratified | 0.398 (0.308, 0.514) | NA |
| Stratified (derived) log-rank p-value | <.0001 | NA |
| Hazard ratio (95% CI), stratified (derived) | 0.406 (0.313, 0.525) | NA |
| Unstratified log-rank p-value | <.0001 | NA |
| Hazard ratio (95% CI), unstratified | 0.423 (0.328, 0.544) | NA |
| KM median (95% CI) EFS time (months) | 8.3 (4.5, 15.8) | 2.0 (1.6, 2.8) |
| Min, Max EFS time (months) | 0, 31+ | 0+, 33+ |
| Event | | |
| Disease progression, n (%) | 82 (46) | 75 (42) |
| Best response of SD up to and including Day 150 assessment post-randomization, n (%) | 4 (2) | 0 (0) |

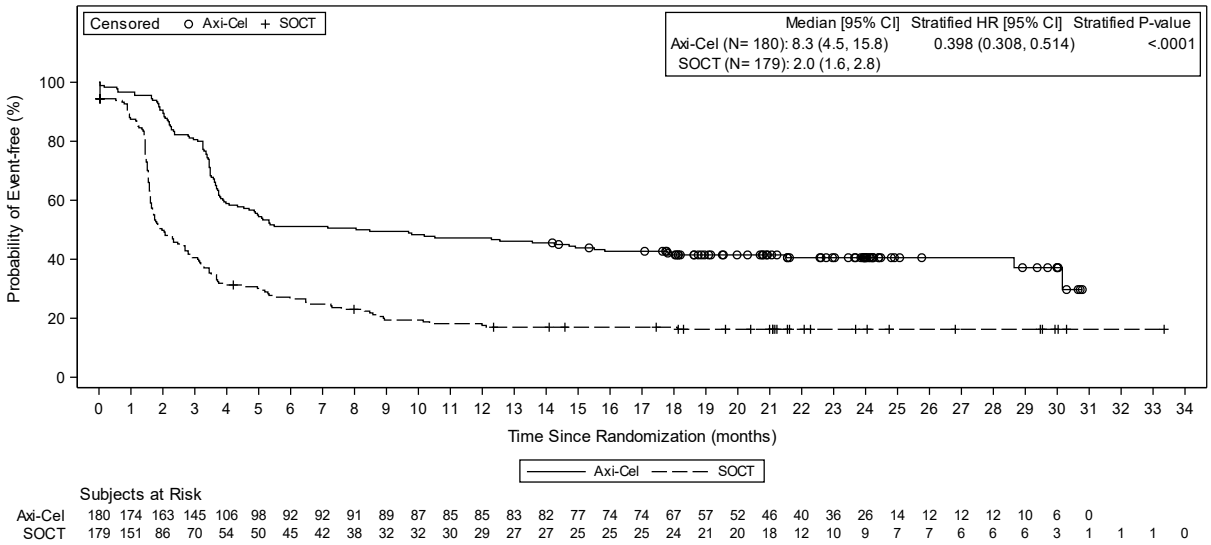
| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| New lymphoma therapy[b], n (%) | 9 (5) | 63 (35) |
| Axicabtagene ciloleucel retreatment, n (%) | 2 (1) | 0 (0) |
| Death from any cause, n (%) | 11 (6) | 6 (3) |
| Censoring reason | | |
| Response ongoing, n (%) | 72 (40) | 28 (16) |
| Response assessed but no disease at baseline and post-baseline, n (%) | 0 (0) | 3 (2) |
| No post-baseline disease assessment, n (%) | 0 (0) | 1 (1) |
| Full withdrawal of consent, n (%) | 0 (0) | 1 (1) |
| Lost to follow up, n (%) | 0 (0) | 2 (1) |
| Event-free rate, % (95% CI) by KME | | |
| 3 month | 80.6 (74.0, 85.6) | 40.5 (33.2, 47.8) |
| 6 month | 51.1 (43.6, 58.1) | 26.6 (20.2, 33.3) |
| 9 month | 49.4 (42.0, 56.5) | 19.4 (13.8, 25.6) |
| 12 month | 47.2 (39.8, 54.3) | 17.6 (12.3, 23.6) |
| 15 month | 43.9 (36.5, 50.9) | 17.0 (11.8, 23.0) |
| 18 month | 41.5 (34.2, 48.6) | 17.0 (11.8, 23.0) |
| 21 month | 41.5 (34.2, 48.6) | 16.3 (11.1, 22.2) |
| 24 month | 40.5 (33.2, 47.7) | 16.3 (11.1, 22.2) |
| 27 month | 40.5 (33.2, 47.7) | 16.3 (11.1, 22.2) |
| 30 month | 37.2 (28.0, 46.3) | 16.3 (11.1, 22.2) |
| 33 month | NE (NE, NE) | 16.3 (11.1, 22.2) |
| Median (95% CI) follow-up time (months) (reverse KM approach) | 23.0 (20.9, 24.0) | 21.2 (20.4, 23.7) |

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; EFS, event-free survival; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; SCT, stem cell transplant; SD, stable disease.
Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy (including SCT in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. The derived stratification factors are based on data collected on case report forms. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

a. Only 8 subjects (all in the standard of care therapy arm) of a total of 359 subjects were censored before Month 12 (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Listing 16.2.1.1).

b. A total of 12 subjects (2 in the axicabtagene ciloleucel arm and 10 in the standard of care therapy arm) initiated a new lymphoma therapy in the absence of any post-baseline evaluable disease assessment (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Listings 16.2.1.1 and 16.2.1.2) and had EFS event dates imputed as the randomization date as predefined in the statistical analysis plan.

**Figure 5. Kaplan-Meier Plot of EFS per Blinded Central Assessment (Full Analysis Set)**




Data cutoff date = 18MAR2021.
Abbreviations: Axi-cel, axicabtagene ciloleucel; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; SOCT, standard of care therapy.
Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy (including stem cell transplant in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause.
The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified Cox regression models are used to provide the estimated HR and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months). Only 8 subjects (all in the SOCT arm) of a total of 359 subjects were censored before Month 12 (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Listing 16.2.1.1). A total of 12 subjects (2 in the axicabtagene ciloleucel arm and 10 in the SOCT arm) initiated a new lymphoma therapy in the absence of any post-baseline evaluable disease assessment (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Listings 16.2.1.1 and 16.2.1.2) and had EFS event dates imputed as the randomization date as predefined in the statistical analysis plan.

## Subgroup Analyses of EFS

The EFS rate for each treatment arm, using blinded central assessment of response, was further analyzed in subgroups defined by selected baseline demographic and disease characteristics. For subgroups wherein few subjects were included, data should be interpreted with caution.

Across the majority of subgroup categories, axicabtagene ciloleucel was favored over SOCT.

For the randomization stratification factor of response to first-line therapy, trends were similar between IxRS data and data derived from the clinical database. Subjects with derived relapse ≤ 12 months of completion of first-line therapy (relapse ≤ 6 months of first-line therapy and relapse > 6 and ≤ 12 months of first-line therapy subgroups were collapsed due to low subject numbers) had a median EFS time per central assessment in the axicabtagene ciloleucel and SOCT arms of not reached (NR) (95% CI: 14.3 months, not estimable; n = 46) and 3.7 months (95% CI: 2.0, 6.5 months; n = 46), respectively; with a stratified HR of 0.306 (95% CI: 0.178, 0.528). In comparison, subjects who were refractory to first-line therapy had a median EFS time in the axicabtagene ciloleucel and SOCT arms of 4.3 months (95% CI: 3.6, 8.0 months; n = 133) and 1.7 months (95% CI: 1.6, 2.3 months; n = 132), respectively; with a stratified HR of 0.443 (95% CI: 0.332, 0.591).

For the randomization stratification factor of sAAIPI (data derived from the clinical database), median EFS time per central assessment for subjects with a score of 0 to 1 in the axicabtagene ciloleucel and

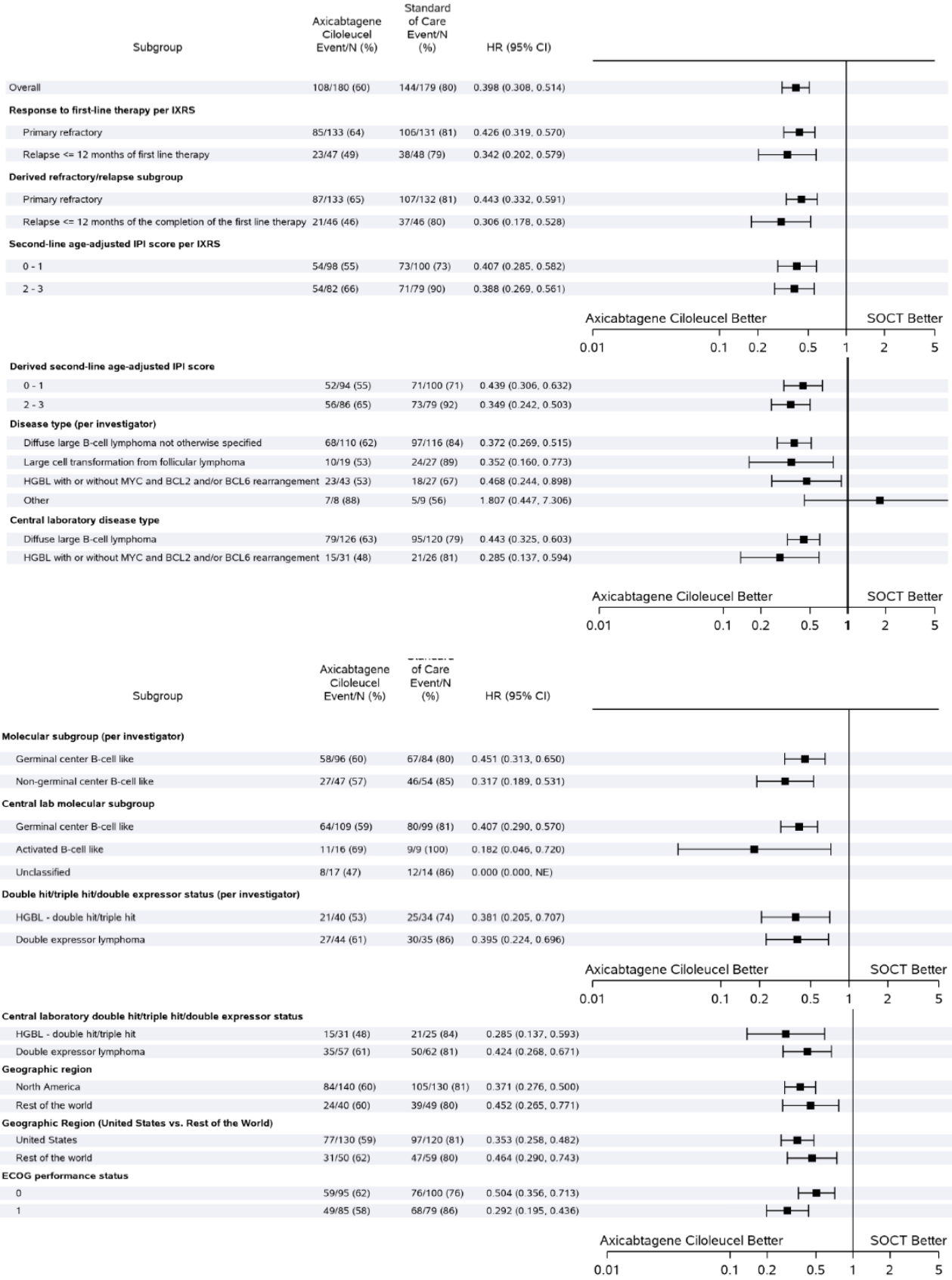
SOCT arms was 14.3 months (95% CI: 5.1 months, not estimable; n = 94) and 2.6 months (95% CI: 1.7, 3.4 months; n = 100), respectively, with a stratified HR of 0.439 (95% CI: 0.306, 0.632). In comparison, the median EFS time for subjects with a score of 2 to 3 in the axicabtagene ciloleucel and SOCT arms was 4.9 months (95% CI: 3.7, 13.6 months; n = 86) and 1.7 months (95% CI: 1.6, 2.3 months; n = 79), respectively, with a stratified HR of 0.349 (95% CI: 0.242, 0.503).

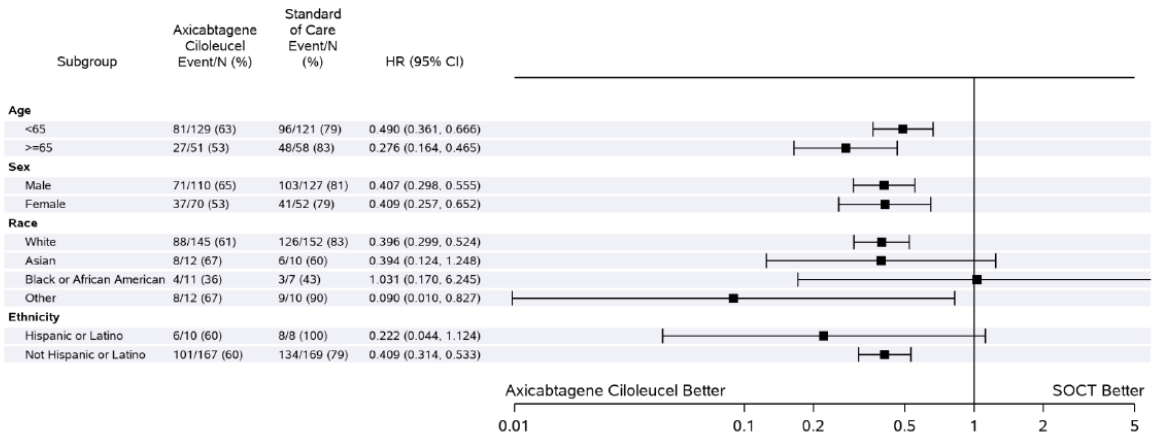
For disease subtype as determined by the investigator, the median EFS time per central assessment for subjects with DLBCL, NOS, in the axicabtagene ciloleucel and SOCT arms was 5.4 months (95% CI: 3.9, 14.9 months; n = 110) and 1.8 months (95% CI: 1.6, 2.7 months; n = 116), respectively, with a stratified HR of 0.372 (95% CI: 0.269, 0.515). Subjects with large cell transformation of FL in the axicabtagene ciloleucel and SOCT arms had a median EFS time of 28.6 months (95% CI: 3.6 months, not estimable; n = 19) and 2.7 months (95% CI: 1.6, 7.3; n = 27), respectively, with a stratified HR of 0.352 (95% CI: 0.160, 0.773). Subjects with HGBL (with or without *MYC* and *BCL2* and/or *BCL6* rearrangements) in the axicabtagene ciloleucel and SOCT arms had a median EFS time of 21.5 months (95% CI: 3.7 months, not estimable; n = 43) and 2.1 months (95% CI: 1.5, 6.6 months; n = 27), respectively, with a stratified HR of 0.468 (95% CI: 0.244, 0.898).
For disease subtype as determined by the central laboratory, median EFS time per central assessment for subjects with DLBCL (including DLBCL, NOS, and DLBCL without further classification possible) in the axicabtagene ciloleucel and SOCT arms was 5.4 months (95% CI: 3.8, 15.5 months; n = 126) and 2.3 months (95% CI: 1.7, 3.2 months; n = 120), respectively, with a stratified HR of 0.443 (95% CI: 0.325, 0.603). Subjects with HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangements in the axicabtagene ciloleucel and SOCT arms had a median EFS time of 21.5 months (95% CI: 3.7 months, not estimable; n = 31) and 1.6 months (95% CI: 1.5, 3.9 months; n = 26), respectively, with a stratified HR of 0.285 (95% CI: 0.137, 0.594).

For the high-risk factor of rearrangement of or overexpression of *MYC* and *BCL-2* and/or *BCL6*, double- or triple-hit or double-expressor status was determined by the central laboratory and median EFS was determined by central assessment. Subjects with HGBL double- or triple-hit lymphomas in the axicabtagene ciloleucel and SOCT arms had a median EFS time of 21.5 months (95% CI: 3.7 months, not estimable; n = 31) and 1.6 months (95% CI: 1.5, 3.9 months; n = 25), respectively, with a stratified HR of 0.285 (95% CI: 0.137, 0.593). Subjects with double-expressor lymphomas in the axicabtagene ciloleucel and SOCT arms had a median EFS time of 7.2 months (95% CI: 3.7 months, not estimable; n = 57) and 2.7 months (95% CI: 1.7, 3.5 months; n = 62), respectively, with a stratified HR of 0.424 (95% CI: 0.268, 0.671).

For the high-risk factor of older age, subjects ≥ 65 years of age in the axicabtagene ciloleucel and SOCT arms had a median EFS time per central assessment of 21.5 months (95% CI: 5.0 months, not estimable; n = 51) and 2.5 months (95% CI: 1.6, 3.2 months; n = 58), respectively, with a stratified HR of 0.276 (95% CI: 0.164, 0.465). In comparison, subjects < 65 years of age in the axicabtagene ciloleucel and SOCT arms had a median EFS time of 5.1 months (95% CI: 3.6, 14.7 months; n = 129) and 1.8 months (95% CI: 1.6, 2.9 months; n = 121), respectively, with a stratified HR of 0.490 (95% CI: 0.361, 0.666).

**Figure 6. Forest Plot of EFS by Subgroups per Central Assessment (FAS)**






Data Cutoff Date = 18MAR2021.
Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FAS, full analysis set; HR, hazard ratio; IxRS, interactive voice/web response system; NE, not estimable; SOCT, standard of care therapy.
Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy (including stem cell transplant in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and/or second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via IxRS. Stratified Cox regression models are used to provide the estimated HR and 2-sided 95% CIs for axicabtagene ciloleucel relative to SOCT. The Breslow method is used to handle the ties for the Cox regression models. Disease type of "Other" includes T cell/histiocyte rich large B cell lymphoma, Epstein-Barr virus (EBV) + DLBCL, primary cutaneous DLBCL (leg type), and other types. HGBL – double hit is defined as presence of *MYC* and either *BCL2* or *BCL6* rearrangements; HGBL - triple hit is defined as presence of *BCL2*, *BCL6*, and *MYC* rearrangements; double-expressor lymphoma is defined as overexpression of MYC and BCL2 proteins not related to underlying chromosomal rearrangements. In the central laboratory molecular unclassified subgroup, the number of subjects and/or number of events are sparse across stratification factors between the treatment arms and resulted in an estimated HR < 0.00001.
Source: Figure 14.2.1.2.1.

- **Key Secondary Efficacy Endpoints: ORR and OS**

**1. ORR per Blinded Central Assessment**

ORR was higher in the axicabtagene ciloleucel arm (83% of subjects) than in the SOCT arm (50% of subjects), with a statistically significant difference in ORR between the treatment arms of 33.1% (95% CI: 23.2%, 42.1%; stratified CMH p < 0.0001; odds ratio = 5.31 [95% CI: 3.08, 8.90; stratified CMH test p < 0.0001). The CR rate was also numerically higher in the axicabtagene ciloleucel arm (65%) compared with the SOCT arm (32%).

**Table 7. Summary of ORR and Best Overall Response per Blinded Central Assessment (Full Analysis Set)**

| Response Category | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Number of objective responders (CR + PR), n (%) | 150 (83) | 90 (50) |
| 95% CI for ORR | (77.1, 88.5) | (42.7, 57.8) |
| Difference in ORR (95% CI) | 33.1 (23.2, 42.1) | NA |
| Stratified CMH test p-value | <.0001 | NA |
| Complete response, n (%) | 117 (65) | 58 (32) |
| 95% CI for response rate | (57.6, 71.9) | (25.6, 39.8) |
| Partial response, n (%) | 33 (18) | 32 (18) |
| 95% CI for response rate | (13.0, 24.8) | (12.6, 24.3) |
| Stable disease, n (%) | 5 (3) | 33 (18) |
| 95% CI for response rate | (0.9, 6.4) | (13.0, 24.9) |
| Progressive disease, n (%) | 21 (12) | 38 (21) |
| 95% CI for response rate | (7.4, 17.3) | (15.5, 28.0) |
| Undefined/ no disease, n (%) | 0 (0) | 4 (2) |

| Response Category | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| 95% CI for response rate | (0.0, 2.0) | (0.6, 5.6) |
| Not evaluable, n (%) | 0 (0) | 0 (0) |
| 95% CI for response rate | (0.0, 2.0) | (0.0, 2.0) |
| Not done, n (%) | 4 (2) | 14 (8) |
| 95% CI for response rate | (0.6, 5.6) | (4.3, 12.8) |

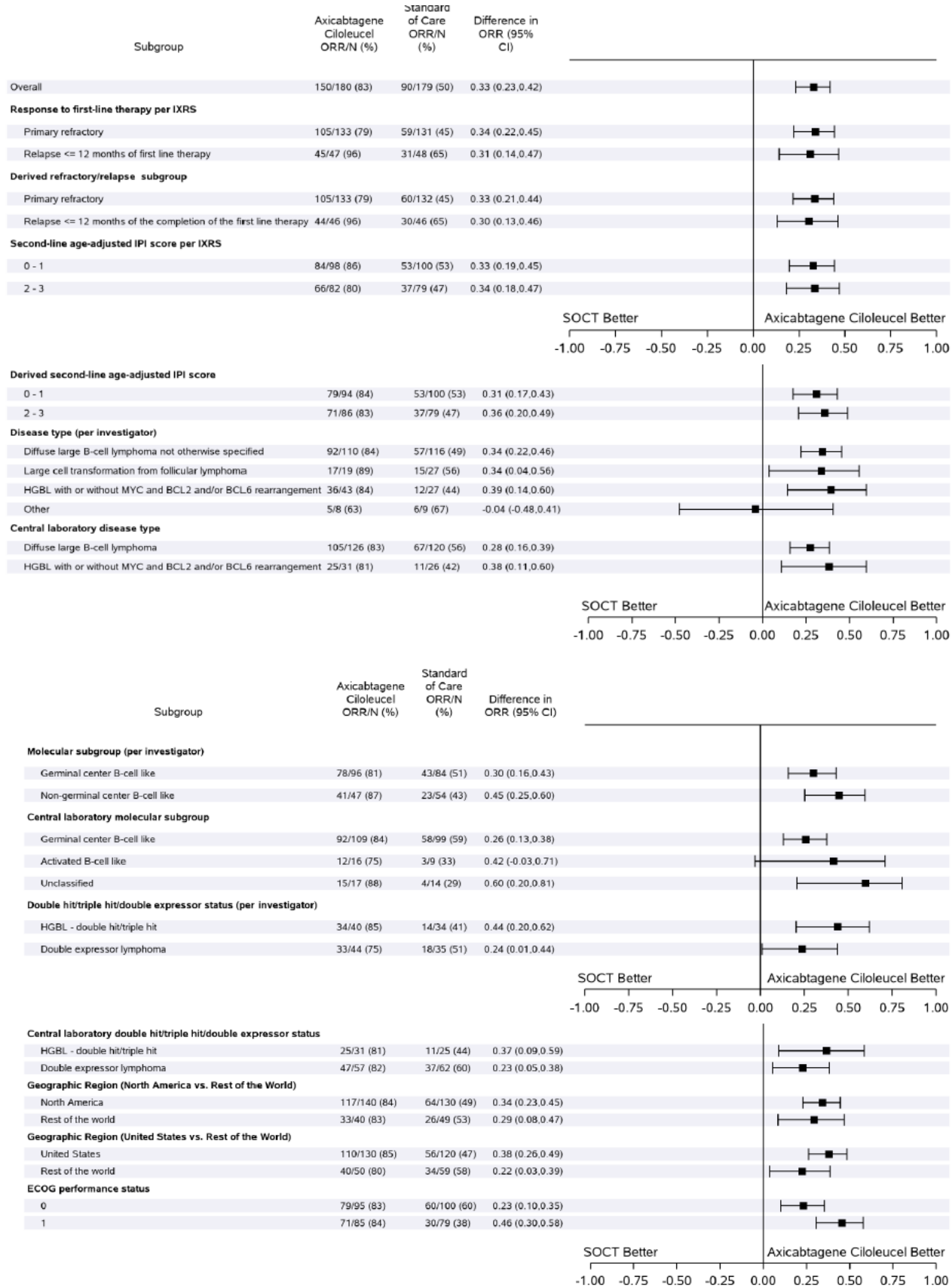
Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; NA, not applicable; ORR, objective response rate; PR, partial response.
Notes: 95% CI for rate is from the Clopper-Pearson method, and the 95% CI for the difference in ORR (standard of care therapy arm as reference group) is from Wilson's score method with continuity correction. Response assessments per Lugano Classification {Cheson 2014}. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. One-sided p-value from CMH test is presented. "Undefined/no disease" include subjects who were found to have no disease at baseline or follow-up by central assessment but had disease by investigator assessment. "Not evaluable" disease assessments were performed but no conclusion could be made.

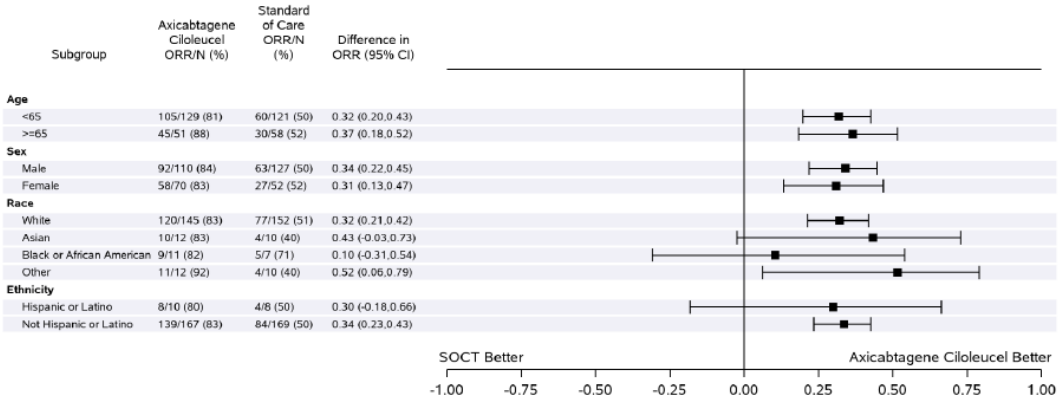
Concordance between the investigator and blinded central assessment of ORR was high at 89% (κ = 0.76; 95% CI: 0.69, 0.83). Sensitivity analysis of ORR per investigator assessment was consistent with the ORR results based on blinded central assessment, with a difference in ORR between arms of 38.1% (95% CI: 28.1%, 47.0%).

Subgroup analysis of ORR per Blinded Central Assessment

In the majority of subgroups, differences in ORR were consistent with the FAS, favoring axicabtagene ciloleucel over SOCT. Data should be interpreted with caution for subgroups that included few subjects. Subgroup analysis of differences in CR rate were consistent with ORR subgroup analysis.

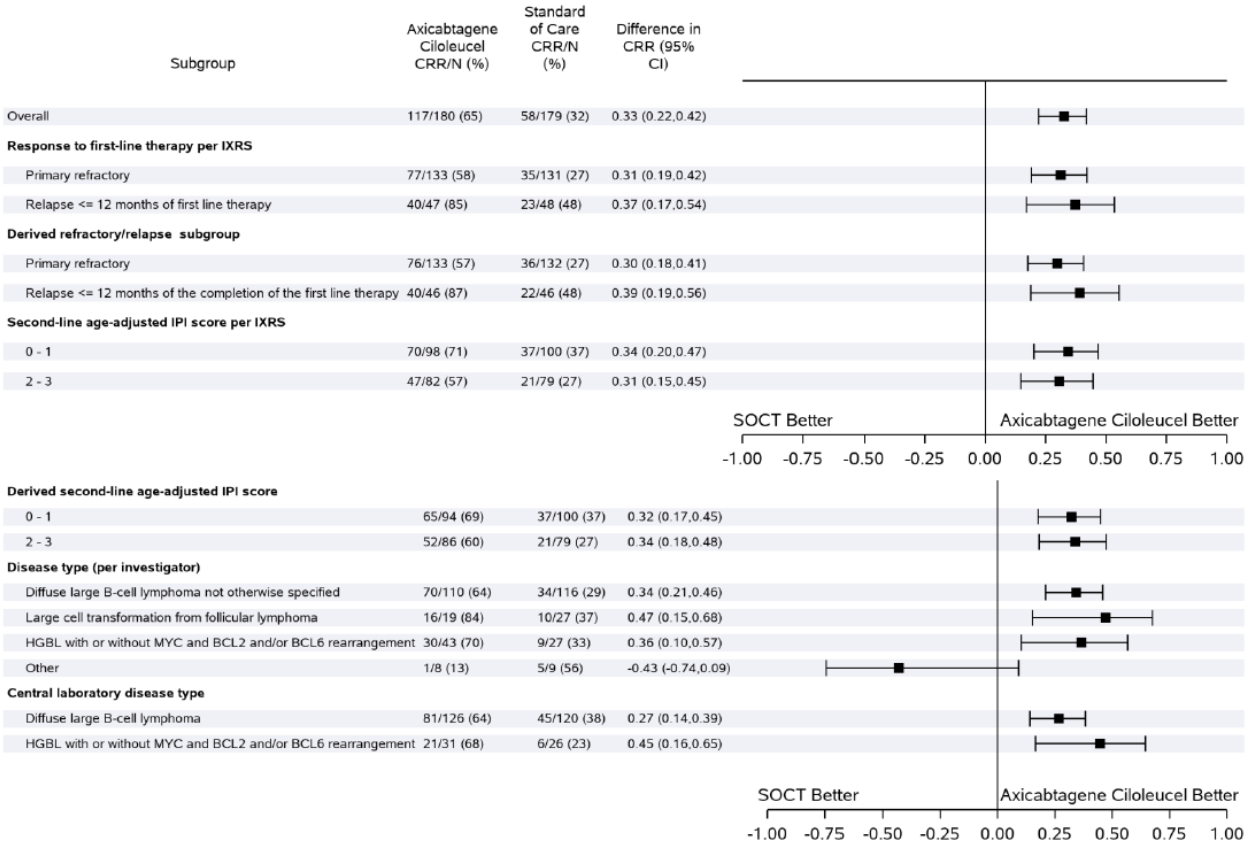
**Figure 7. Forest Plot for Subgroup Analysis of ORR Difference per Blinded Central Assessment (Full Analysis Set)**

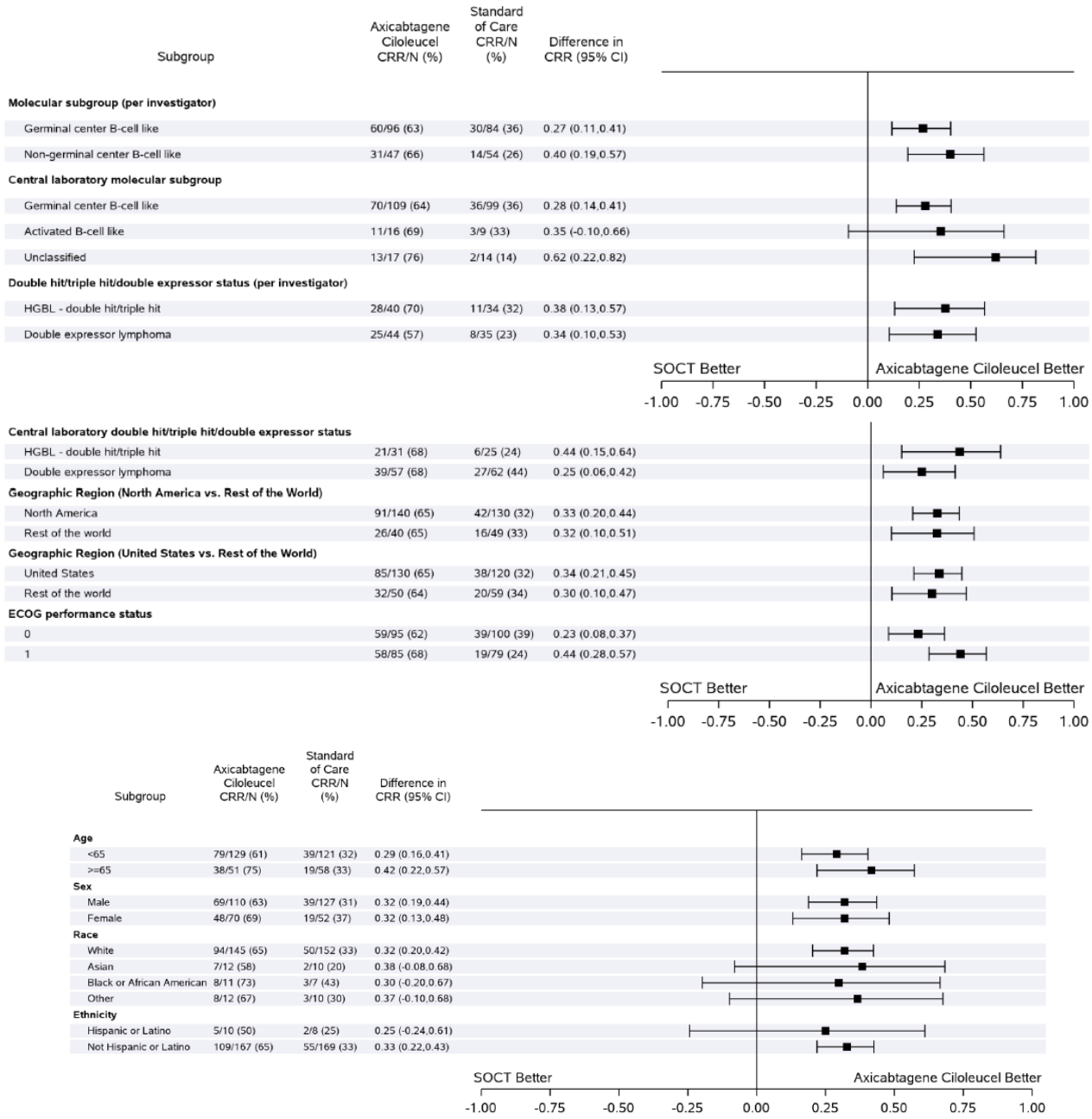





Data Cutoff Date = 18MAR2021.
Abbreviations: CI, confidence interval; IxRS, interactive voice/web response system; ORR, Objective Response Rate; SOCT, standard of care therapy.
Notes: 95% CI for the difference in ORR (SOCT arm as reference group) is from Wilson's score method with continuity correction. ORR is defined as the incidence of either a complete response or a partial response by the Lugano Classification {Cheson 2014}. Disease type of "Other" includes T cell/histiocyte rich large B cell lymphoma, Epstein-Barr virus (EBV) + DLBCL, primary cutaneous DLBCL (leg type), and other types. HGBL – double hit is defined as presence of *MYC* and either *BCL2* or *BCL6* rearrangements; HGBL - triple hit is defined as presence of *BCL2*, *BCL6*, and *MYC* rearrangements; double-expressor lymphoma is defined as overexpression of MYC and BCL2 proteins not related to underlying chromosomal rearrangements.
Source: Figure 14.2.2.1.1.

**Figure 8. Forest Plot of CR Rate Difference by Subgroups per Central Assessment (FAS)**






Data Cutoff Date = 18MAR2021.
Abbreviations: CI, Confidence Interval; CRR, Complete Response Rate; IxRS, interactive voice/web response system; SOCT, standard of care therapy.
Notes: 95% CI for the difference in CRR (SOCT arm as reference group) is from Wilson's score method with continuity correction. ORR is defined as the incidence of either a complete response or a partial response by the Lugano Classification {Cheson 2014}. Disease type of "Other" includes T cell/histiocyte rich large B cell lymphoma, Epstein-Barr virus (EBV) + DLBCL, primary cutaneous DLBCL (leg type), and other types. HGBL – double hit is defined as presence of MYC and either BCL2 or BCL6 rearrangements; HGBL - triple hit is defined as presence of BCL2, BCL6, and MYC rearrangements; double expressor lymphoma is defined as overexpression of MYC and BCL-2 proteins not related to underlying chromosomal rearrangements.
Source: Figure 14.2.2.2.1.

## 2. OS

After significant improvement in EFS and ORR was demonstrated in the axicabtagene ciloleucel arm over the SOCT arm, the interim analysis of OS was to assess the difference between treatment arms using log-rank tests stratified by randomization factors.

After the EFS primary analysis data cutoff date, Kite obtained additional survival follow-up for subjects discontinued from ZUMA-7 and that was not available at the time of the interim OS analysis (which was conducted at the time of the EFS primary analysis) but occurred before the data cutoff date of 18 March

2021. At the time of the data cutoff, 72 subjects (40%) in the axicabtagene ciloleucel arm and 85 subjects (47%) in the SOCT arm had died (stratified HR of 0.708 [95% CI: 0.515, 0.972]). In the axicabtagene ciloleucel arm the KM estimated median OS had not been reached with a median follow-up time for OS (reverse KM approach) of 24.7 months (95% CI: 23.3, 26.0). In the SOCT arm the KM estimated median OS was 25.7 months with a median follow-up time for OS of 24.4 month (95% CI: 22.5, 25.7).

While the data are still immature, the interim analysis of OS favored axicabtagene ciloleucel over SOCT, but the difference between the treatment arms was not statistically significant (p = 0.0159 with a 1-sided alpha of 0.004 allocated to the interim OS analysis).

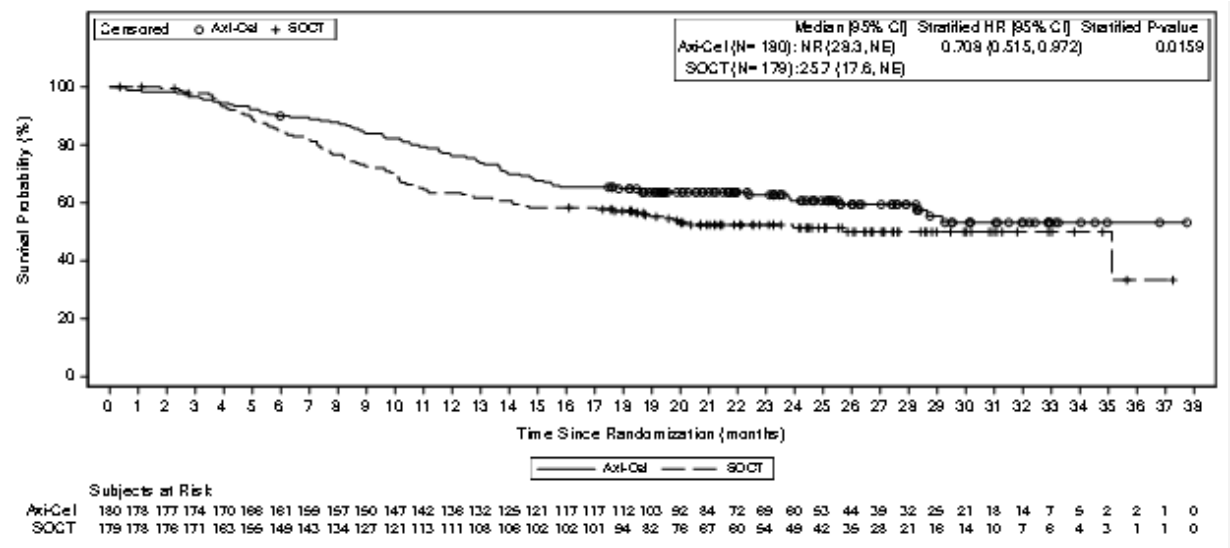
**Table 8. Overall Survival (Additional Publicly Available Information) (Full Analysis Set)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care Therapy (N = 179) |
|---|---|---|
| Number of subjects | 180 | 179 |
| Death from any cause, n (%) | 72 (40) | 85 (47) |
| Alive, n (%) | 108 (60) | 94 (53) |
| Full consent withdrawn | 0 (0) | 5 (3) |
| Lost to follow up | 1 (1) | 0 (0) |
| End of study due to investigator decision | 0 (0) | 0 (0) |
| End of study due to other reason | 0 (0) | 0 (0) |
| Stratified log-rank p-value | 0.0159 | NA |
| Hazard ratio (95% CI), stratified | 0.708 (0.515, 0.972) | NA |
| Unstratified log-rank p-value | 0.0275 | NA |
| Hazard ratio (95% CI), unstratified | 0.736 (0.538, 1.008) | NA |
| KM median (95% CI) OS time (months) | NR (28.3, NE) | 25.7 (17.6, NE) |
| Min, Max OS time (months) | 1, 38+ | 0+, 37+ |
| Survival rate % (95% CI) by KME | | |
| 3 month | 96.7 (92.7, 98.5) | 97.7 (94.1, 99.1) |
| 6 month | 90.0 (84.6, 93.6) | 85.2 (79.0, 89.6) |
| 9 month | 83.9 (77.6, 88.5) | 72.6 (65.3, 78.6) |
| 12 month | 76.0 (69.1, 81.6) | 63.4 (55.8, 70.1) |
| 15 month | 67.6 (60.3, 74.0) | 58.3 (50.6, 65.2) |
| 18 month | 64.8 (57.4, 71.3) | 57.1 (49.4, 64.1) |
| 21 month | 63.6 (56.1, 70.2) | 52.4 (44.6, 59.6) |
| 24 month | 60.7 (52.8, 67.7) | 51.3 (43.4, 58.7) |
| 27 month | 59.4 (51.3, 66.7) | 49.9 (41.8, 57.5) |
| 30 month | 53.2 (43.1, 62.2) | 49.9 (41.8, 57.5) |
| 33 month | 53.2 (43.1, 62.2) | 49.9 (41.8, 57.5) |
| 36 month | 53.2 (43.1, 62.2) | 33.3 (9.9, 59.2) |

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care Therapy (N = 179) |
|---|---|---|
| Median (95% CI) follow-up time (months) (reverse KM approach) | 24.7 (23.3, 26.0) | 24.4 (22.5, 25.7) |

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; NR, not reached; OS, overall survival.
Notes: OS is defined as the time from the randomization date to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date will be censored at the data cutoff date.
The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system.
Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy.
One-sided p-value from log-rank test is presented.
Censored times are represented with a "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/Censoring time was calculated as Event/Censoring date – Randomization date +1 (= days) / 30.4375 (= months).

**Figure 9. Kaplan-Meier Plot of Overall Survival (Additional Publicly Available Information) (Full Analysis Set)**

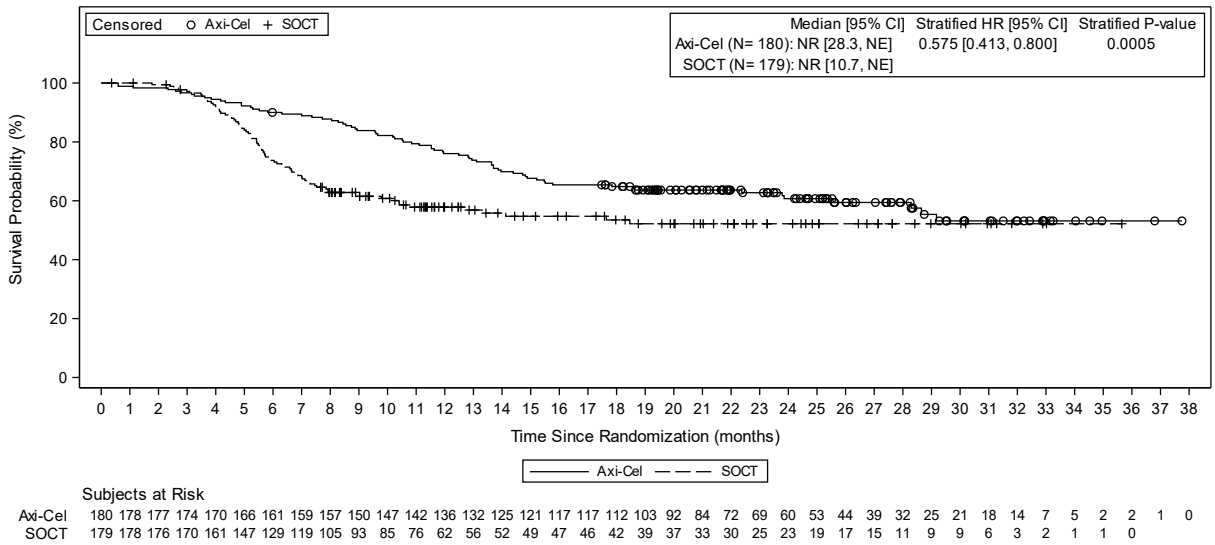



Data Cutoff Date = 18MAR2021.
Abbreviations: axi-cel, axicabtagene ciloleucel; CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached; SOCT, standard of care therapy.
Notes: Overall survival is defined as the time from the randomization date to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date will be censored at the data cutoff date.
The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system.
Stratified Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care. The Breslow method is used to handle the ties for the Cox regression models.
One-sided p-value from log-rank test is presented.
Event/Censoring time was calculated as Event/Censoring date – Randomization date +1 (= days) / 30.4375 (= months).

Although there was no planned crossover between treatment arms, subjects who did not respond to SOCT could receive subsequent treatment for lymphoma deemed appropriate by the investigator, such as non-study specific chemotherapy, immunotherapy, targeted agents, as well as anti-CD19 CAR T-cell therapy off protocol. Of the 179 subjects randomized to the SOCT arm, 100 subjects (56%) later

received commercially available or investigational cell therapy as new lymphoma therapy after SOCT (ie, treatment switching rate). Sensitivity analyses of OS were performed to address the confounding effects from subsequent cell therapy in the SOCT arm. The sensitivity analysis results reinforced the positive trend seen for OS in the FAS.

**Figure 10. KM Plot of OS – With Additional Publicly Available Information for Discontinued Subjects – Sensitivity Analysis 1 (Full Analysis Set)**

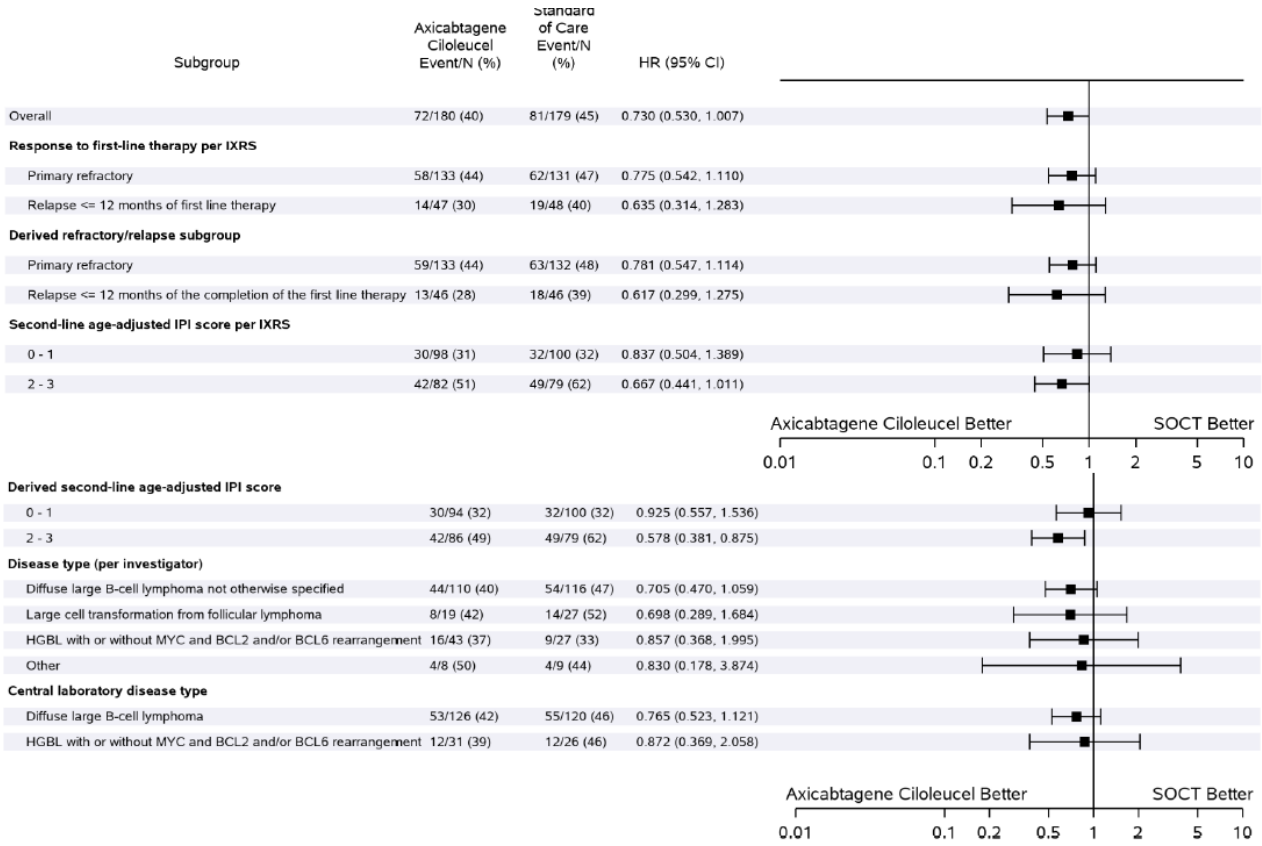


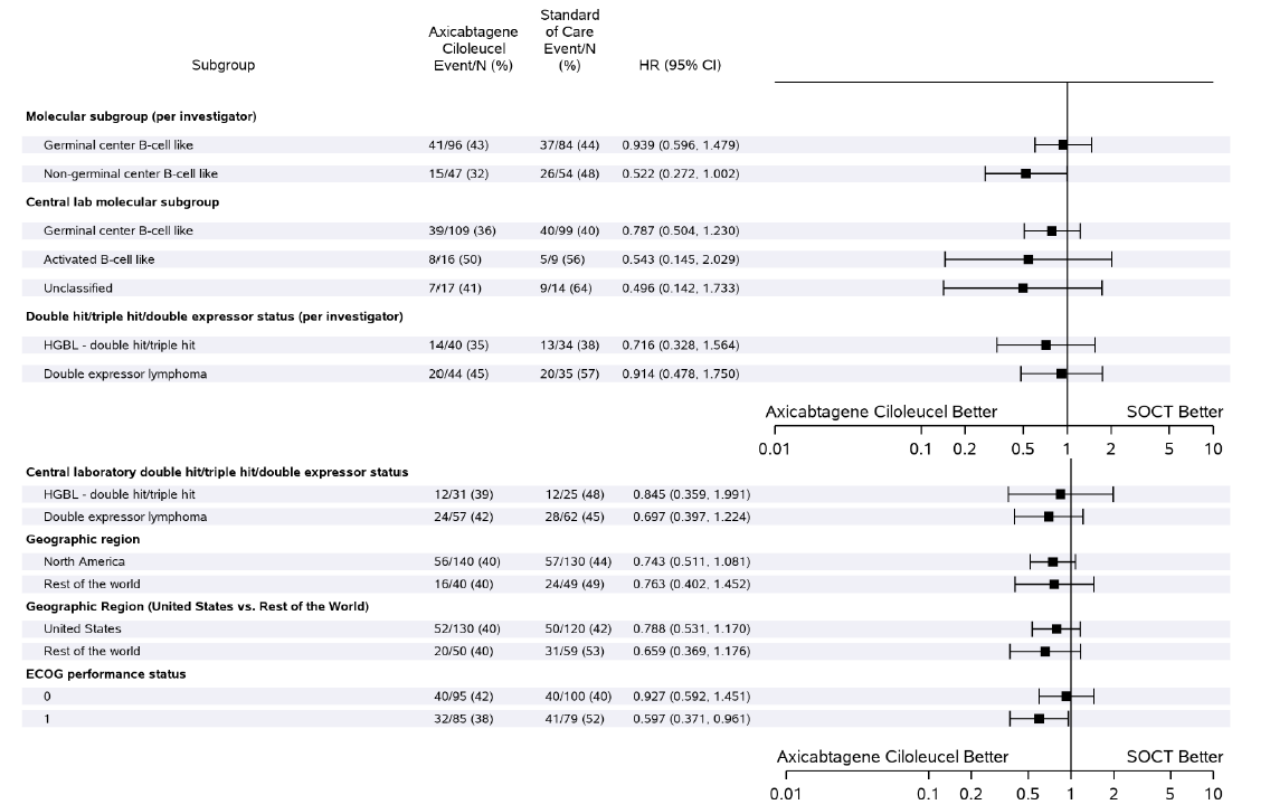

Data Cutoff Date = 18MAR2021.
Abbreviations: Axi-Cel, axicabtagene ciloleucel; CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached; SOCT, standard of care therapy.
Notes: Per sensitivity analysis #1: Rank preserving structural failure time model {Robins 1991} was used to adjust treatment drop in from standard of care to chimeric antigen receptor T-cell therapy.
OS is defined as the time from the randomization date to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date will be censored at the data cutoff date.
The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system.
Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy.
One-sided p-value from log rank test is presented.

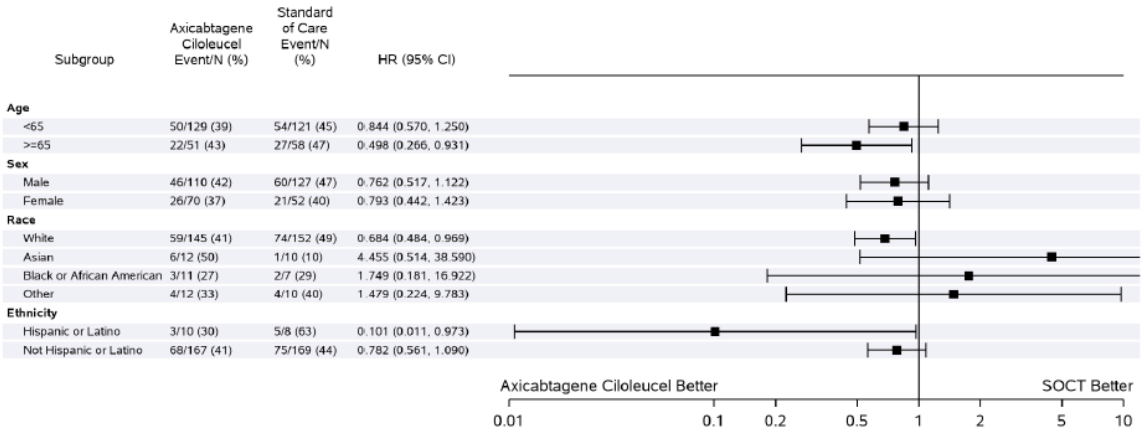
Subgroup analysis of OS

Across the majority of subgroup categories, axicabtagene ciloleucel was favored over SOCT.

**Figure 11. Forest Plot of OS by Subgroups (FAS)**






Data Cutoff Date = 18MAR2021.
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HGBL, high-grade B-cell lymphoma; HR, hazard ratio; IxRS, interactive voice/web response system; NE, not estimable; SOCT, standard of care therapy.
Notes: Overall survival is defined as the time from the randomization date to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date will be censored at the data cutoff date. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and/or second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via IxRS. Stratified (or unstratified) Cox Regression models are used to provide the estimated HR and 2-sided 95% CIs for axicabtagene ciloleucel relative to SOCT HR. The Breslow method is used to handle the ties for the Cox regression models. Disease type of "Other" includes T cell/histiocyte rich large B cell lymphoma, Epstein-Barr virus (EBV) + DLBCL, primary cutaneous DLBCL (leg type), and other types. HGBL – double hit is defined as presence of *MYC* and either *BCL2* or *BCL6* rearrangements; HGBL - triple hit is defined as presence of *BCL2*, *BCL6*, and *MYC* rearrangements; double-expressor lymphoma is defined as overexpression of MYC and BCL2 proteins not related to underlying chromosomal rearrangements.
Source: Figure 14.2.5.2.

**Other Secondary Efficacy Endpoints**

**1. PFS per Investigator Assessment**

The KM median PFS time based on the investigator assessment was longer in the axicabtagene ciloleucel arm compared with the SOCT arm (14.7 months [95% CI: 5.4, not estimable] versus 3.7 months [95% CI: 2.9, 5.3]) (stratified HR of 0.490 [95% CI: 0.368, 0.652]). The median follow-up time for PFS using the reverse KM method was 22.6 months (95% CI: 20.8, 24.0) in the axicabtagene ciloleucel arm and 19.6 months (95% CI: 14.6, 21.2) in the SOCT arm.

**Table 9. PFS per Investigator Assessment (Full Analysis Set)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Number of subjects | 180 | 179 |
| Events, n (%) | 96 (53) | 103 (58) |
| Censored, n (%) | 84 (47) | 76 (42) |
| Stratified log-rank p-value | <.0001 | NA |
| Hazard ratio (95% CI), stratified | 0.490 (0.368, 0.652) | NA |
| Unstratified log-rank p-value | <.0001 | NA |
| Hazard ratio (95% CI), unstratified | 0.524 (0.396, 0.694) | NA |
| KM median (95% CI) PFS time (months) | 14.7 (5.4, NE) | 3.7 (2.9, 5.3) |
| Min, Max PFS time (months) | 0+, 31+ | 0+, 33+ |
| Event | | |
| Disease progression, n (%) | 85 (47) | 98 (55) |
| Death from any cause, n (%) | 11 (6) | 5 (3) |
| Censoring reason | | |

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Response ongoing, n (%) | 79 (44) | 34 (19) |
| New lymphoma therapy, n (%) | 5 (3) | 37 (21) |
| No post-baseline disease assessment, n (%) | 0 (0) | 1 (1) |
| Full withdrawal of consent, n (%) | 0 (0) | 2 (1) |
| Lost to follow up, n (%) | 0 (0) | 2 (1) |
| Progression-free rate, % (95% CI) by KME | | |
| 3 month | 87.6 (81.7, 91.6) | 57.3 (49.0, 64.8) |
| 6 month | 57.2 (49.6, 64.2) | 39.3 (31.1, 47.3) |
| 9 month | 55.5 (47.9, 62.5) | 31.7 (23.9, 39.7) |
| 12 month | 52.1 (44.4, 59.2) | 28.2 (20.8, 36.2) |
| 15 month | 49.2 (41.6, 56.3) | 27.4 (20.0, 35.3) |
| 18 month | 46.7 (39.1, 53.9) | 27.4 (20.0, 35.3) |
| 21 month | 46.7 (39.1, 53.9) | 27.4 (20.0, 35.3) |
| 24 month | 45.7 (38.1, 53.0) | 27.4 (20.0, 35.3) |
| 27 month | 45.7 (38.1, 53.0) | 27.4 (20.0, 35.3) |
| 30 month | 41.9 (31.9, 51.6) | 27.4 (20.0, 35.3) |
| 33 month | NE (NE, NE) | 27.4 (20.0, 35.3) |
| Median (95% CI) follow-up time (months) (reverse KM approach) | 22.6 (20.8, 24.0) | 19.6 (14.6, 21.2) |

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; PFS, progression-free survival; SCT, stem cell transplant.
Notes: PFS is defined as the time from the randomization date to the date of disease progression or death from any cause. Subjects not meeting the criteria by the analysis data cutoff date will be censored at their last evaluable disease assessment date prior to the data cutoff date or new lymphoma therapy start date (including SCT in the axicabtagene ciloleucel arm or retreatment of axicabtagene ciloleucel), whichever is earlier. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

**2. DOR per blinded central assessment**

The median DOR among responders was longer in the axicabtagene ciloleucel arm at 26.9 months (95% CI: 13.6, not estimable) compared with the SOCT arm at 8.9 months (95% CI: 5.7, not estimable) (stratified HR of 0.736 [95% CI: 0.488, 1.108]), with a median follow-up time for DOR using the reverse KM method of 19.5 months and 17.3 months, respectively.

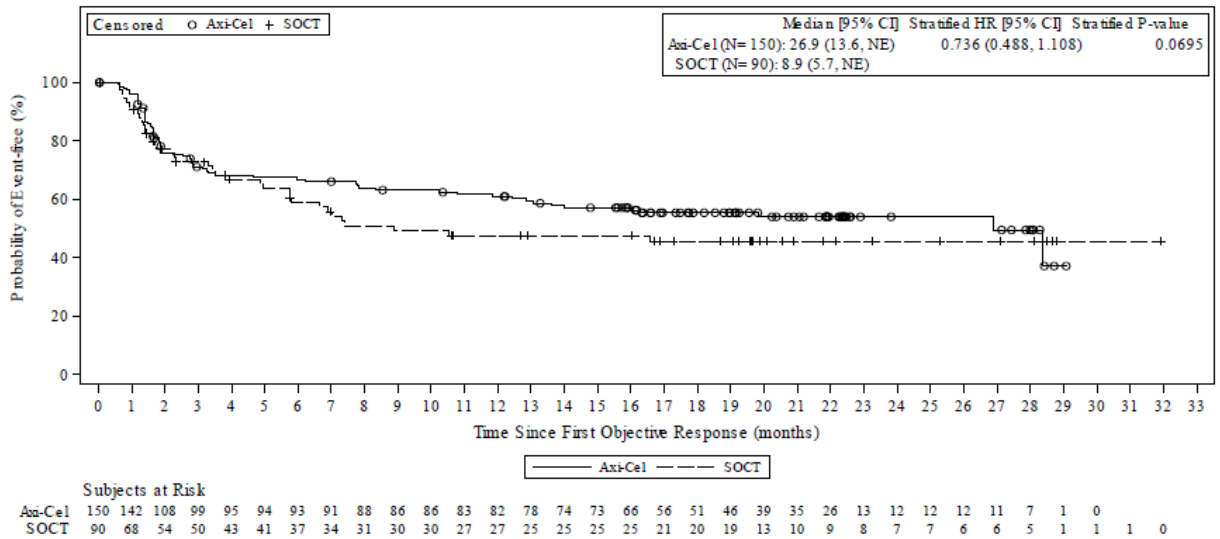
**Table 10. DOR per Blinded Central Assessment (Full Analysis Set)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Number of objective responders (CR + PR) | 150 | 90 |
| Events, n (%) | 66 (44) | 37 (41) |
| Censored, n (%) | 84 (56) | 53 (59) |
| Stratified log-rank p-value | 0.0695 | NA |
| Hazard ratio (95% CI), stratified | 0.736 (0.488, 1.108) | NA |
| Unstratified log-rank p-value | 0.1442 | NA |
| Hazard ratio (95% CI), unstratified | 0.805 (0.537, 1.205) | NA |
| KM median (95% CI) DOR (months) | 26.9 (13.6, NE) | 8.9 (5.7, NE) |
| Min, Max DOR (months) | 0+, 29+ | 0+, 32+ |
| Events | | |
| Disease progression, n (%) | 58 (39) | 34 (38) |
| Death from any cause, n (%) | 8 (5) | 3 (3) |
| Censoring reasons | | |
| Response ongoing, n (%) | 76 (51) | 28 (31) |
| New lymphoma therapy, n (%) | 6 (4) | 23 (26) |
| Subsequent stem cell transplant, n (%) | 0 (0) | 1 (1) |
| Axicabtagene ciloleucel retreatment, n (%) | 2 (1) | 0 (0) |
| Lost to follow up, n (%) | 0 (0) | 1 (1) |
| Event-free rate, % (95% CI) by KME | | |
| 3 month | 71.1 (62.9, 77.7) | 72.7 (60.9, 81.5) |
| 6 month | 66.8 (58.4, 73.8) | 58.9 (46.4, 69.5) |
| 9 month | 63.1 (54.7, 70.5) | 49.2 (36.8, 60.5) |
| 12 month | 60.9 (52.4, 68.4) | 47.6 (35.2, 58.9) |
| 15 month | 57.1 (48.5, 64.8) | 47.6 (35.2, 58.9) |
| 18 month | 55.3 (46.7, 63.2) | 45.6 (33.2, 57.1) |
| 21 month | 54.0 (45.1, 62.0) | 45.6 (33.2, 57.1) |
| 24 month | 54.0 (45.1, 62.0) | 45.6 (33.2, 57.1) |
| 27 month | 49.5 (37.6, 60.3) | 45.6 (33.2, 57.1) |
| 30 month | NE (NE, NE) | 45.6 (33.2, 57.1) |
| Median (95% CI) follow-up time (months) (reverse KM approach) | 19.5 (18.2, 21.7) | 17.3 (12.7, 19.6) |

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; IxRS, interactive voice/web response system; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA; not applicable; NE, not estimable; PR, partial response.
Notes: Percentages are based on number of subjects in the analysis set with objective response. DOR is defined as the time from the first objective response to disease progression per Lugano Classification {Cheson 2014} or death from any cause. Subjects not meeting the criteria by the analysis data cutoff date will be censored at their last evaluable disease assessment date prior to the data cutoff date or new lymphoma therapy start date (including stem cell transplant in the axicabtagene ciloleucel arm or

retreatment of axicabtagene ciloleucel), whichever is earlier. Response assessments per Lugano Classification {Cheson 2014}. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via IxRS. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

**Figure 12. KM Plot of DOR per Central Assessment (FAS)**




Data Cutoff Date = 18MAR2021.
Abbreviations: Axi-cel, axicabtagene ciloleucel; CI, confidence interval; HR, hazard ratio; NE, not estimable; SCT, stem cell transplant; SOCT, standard of care therapy.
Notes: Duration of response is defined as the time from the first objective response to disease progression per Lugano Classification {Cheson 2014} or death from any cause. Subjects not meeting the criteria by the analysis data cutoff date will be censored at their last evaluable disease assessment date prior to the data cutoff date or new lymphoma therapy start date (including SCT in the axicabtagene ciloleucel arm or retreatment of axicabtagene ciloleucel), whichever is earlier. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified Cox regression models are used to provide the estimated HR and 2-sided 95% CIs for axicabtagene ciloleucel relative to SOCT. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log rank test is presented. Event/Censoring time was calculated as Event/Censoring date – Randomization date +1 (= days) / 30.4375 (= months).

**3. mEFS per blinded central assessment**

mEFS was defined the same way as EFS, except that SD as the best response by Study Day 150 assessment was not considered an event.

Based on the blinded central assessment of mEFS, 104 subjects (58%) in the axicabtagene ciloleucel arm and 144 subjects (80%) in the SOCT arm had had an event at the time of the data cutoff (stratified HR of 0.376 [95% CI: 0.290, 0.487]). The KM median mEFS was longer in the axicabtagene ciloleucel arm (10.3 months [95% CI: 5.0, 21.5]) than in the SOCT arm (2.0 months [95% CI: 1.6, 2.8]).

**Table 11. mEFS by Blinded Central Assessment (Full Analysis Set)**

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Number of subjects | 180 | 179 |
| Events, n (%) | 104 (58) | 144 (80) |
| Censored, n (%) | 76 (42) | 35 (20) |
| Stratified log-rank p-value | <.0001 | NA |
| Hazard ratio (95% CI), stratified | 0.376 (0.290, 0.487) | NA |
| Unstratified log-rank p-value | <.0001 | NA |
| Hazard ratio (95% CI), unstratified | 0.399 (0.309, 0.514) | NA |
| KM median (95% CI) mEFS time (months) | 10.3 (5.0, 21.5) | 2.0 (1.6, 2.8) |

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Min, Max mEFS time (months) | 0, 31+ | 0+, 33+ |
| Event | | |
| Disease progression, n (%) | 82 (46) | 75 (42) |
| New lymphoma therapy, n (%) | 9 (5) | 63 (35) |
| Axicabtagene ciloleucel retreatment, n (%) | 2 (1) | 0 (0) |
| Death from any cause, n (%) | 11 (6) | 6 (3) |
| Censoring reason | | |
| Response ongoing, n (%) | 72 (40) | 28 (16) |
| Best response of SD up to and including Day 150 assessment post-randomization, n (%) | 4 (2) | 0 (0) |
| Response assessed but no disease at baseline and post-baseline, n (%) | 0 (0) | 3 (2) |
| No post-baseline disease assessment, n (%) | 0 (0) | 1 (1) |
| Full withdrawal of consent, n (%) | 0 (0) | 1 (1) |
| Lost to follow up, n (%) | 0 (0) | 2 (1) |
| Event-free rate, % (95% CI) by KME | | |
| 3 month | 82.8 (76.4, 87.6) | 40.5 (33.2, 47.8) |
| 6 month | 53.3 (45.8, 60.3) | 26.6 (20.2, 33.3) |
| 9 month | 51.7 (44.1, 58.7) | 19.4 (13.8, 25.6) |
| 12 month | 49.4 (42.0, 56.5) | 17.6 (12.3, 23.6) |
| 15 month | 46.1 (38.7, 53.2) | 17.0 (11.8, 23.0) |
| 18 month | 43.7 (36.3, 50.8) | 17.0 (11.8, 23.0) |
| 21 month | 43.7 (36.3, 50.8) | 16.3 (11.1, 22.2) |
| 24 month | 42.7 (35.3, 49.9) | 16.3 (11.1, 22.2) |
| 27 month | 42.7 (35.3, 49.9) | 16.3 (11.1, 22.2) |
| 30 month | 39.1 (29.7, 48.5) | 16.3 (11.1, 22.2) |
| 33 month | NE (NE, NE) | 16.3 (11.1, 22.2) |
| Median (95% CI) follow-up time (months) (reverse KM approach) | 22.8 (20.9, 24.0) | 21.2 (20.4, 23.7) |

Data cutoff date = 18MAR2021.

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; mEFS, modified event-free survival; Min, minimum; NA, not applicable; NE, not estimable; SCT, stem cell transplant; SD, stable disease.

Notes: mEFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014} commencement of new lymphoma therapy (including SCT in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. Having SD as the best response by Day 150 assessment post-randomization will not be considered as an event. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

**Response to Retreatment**

Overall, 9 subjects were retreated with axicabtagene ciloleucel. After retreatment, 5 subjects had a response per central assessment, with all 5 subjects achieving a CR. Using the investigator assessment of response, 6 subjects had a response and 4 subjects had a CR.

**Subsequent therapies**

**Table 12. Subsequent Therapies (Full Analysis Set)**

| | Axicabtagene Ciloleucel (N = 180) n (%) | Standard of Care Therapy (N = 179) n (%) |
|---|---|---|
| Received any subsequent therapy | 84 (47) | 127 (71) |
| Chemo(immuno)therapy (including anti-CD20 therapy) | 69 (38) | 71 (40) |
| Autologous CD19 CAR T therapy | 11 (6) | 97 (54) |
| HDT+ASCT | 12 (7) | 7 (4) |
| Allogeneic SCT | 13 (7) | 7 (4) |
| Other cellular therapies | 2 (1) | 5 (3) |
| Allogeneic CD19 CAR T therapy | 1 (1) | 1 (1) |
| Autologous CD19/CD22 bispecific CAR T therapy | 0 (0) | 1 (1) |
| CAR NK anti-CD16 | 1 (1) | 0 (0) |
| CD22 CAR T | 0 (0) | 2 (1) |
| cord blood NK | 0 (0) | 1 (1) |
| Antibody drug conjugates (polatuzumab+/-BR) | 26 (14) | 29 (16) |
| BTK inhibitor | 11 (6) | 6 (3) |
| Immunomodulatory agents | 13 (7) | 18 (10) |
| Radiation therapy alone | 15 (8) | 26 (15) |
| Other therapies (not including any anti-CD20) | 40 (22) | 39 (22) |
| 4-1BB agonist | 0 (0) | 1 (1) |
| anti-CCR4 and checkpoint inhibitor | 1 (1) | 0 (0) |
| BCL2 inhibitor | 6 (3) | 2 (1) |
| BET inhibitor | 0 (0) | 1 (1) |
| Bispecific mAb | 7 (4) | 3 (2) |
| Bispecific T-cell Engager | 0 (0) | 2 (1) |
| CD20 and CD3 bispecific mAb | 0 (0) | 1 (1) |
| checkpoint inhibitor | 18 (10) | 12 (7) |
| CRL4-CRBN E3 ubiquitin ligase inhibitor | 1 (1) | 0 (0) |
| DHODH inhibitor | 1 (1) | 0 (0) |
| EED inhibitor | 1 (1) | 0 (0) |
| heat shock protein 90 inhibitor | 0 (0) | 1 (1) |
| immunotherapy NOS | 0 (0) | 1 (1) |
| IP on clinical study NOS | 3 (2) | 0 (0) |
| IRAK4 kinase inhibitor | 0 (0) | 1 (1) |
| mAb anti-CD19 | 1 (1) | 2 (1) |

| | Axicabtagene Ciloleucel (N = 180) n (%) | Standard of Care Therapy (N = 179) n (%) |
|---|---|---|
| mAb anti-CD27 | 4 (2) | 2 (1) |
| MALT-1 inhibitor | 0 (0) | 1 (1) |
| mRNA and checkpoint inhibitor | 1 (1) | 0 (0) |
| mTOR inhibitor and asparaginase | 0 (0) | 1 (1) |
| nuclear export inhibitor | 2 (1) | 0 (0) |
| PDH-KGDH inhibitor | 1 (1) | 0 (0) |
| PI3K and HDAC inhibitor | 1 (1) | 0 (0) |
| PI3K inhibitor | 1 (1) | 1 (1) |
| recombinant fusion CD47 | 0 (0) | 1 (1) |
| steroids | 8 (4) | 16 (9) |
| surgery | 2 (1) | 1 (1) |

Data cutoff date = 18MAR2021.
Abbreviations: ASCT, autologous stem cell transplant; BCL-2, B-cell lymphoma-2; BET, Bromodomain and Extra-Terminal; BTK, Bruton's tyrosine kinase; BR, bendamustine + rituximab; CAR, chimeric antigen receptor; CCR4, C-C Motif Chemokine Receptor 4; CRL4-CRBN, Cullin–RING ubiquitin ligase complex 4-cereblon; DHODH, dihydroorotate dehydrogenase; EED, embryonic ectoderm development protein; HDAC, histone deacetylase; HDT, high-dose chemotherapy; IP, investigational product; IRAK4, interleukin-1 receptor-associated kinase 4; mRNA, messenger ribonucleic acid; NK, natural killer; NOS, not otherwise specified; mAb, monoclonal antibody; MALT-1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; mTOR, mammalian target of rapamycin; NOS, not otherwise specified; PI3K, phosphoinositide 3-kinase; PDH-KGDH, pyruvate dehydrogenase-ketoglutarate dehydrogenase; SCT, stem cell transplant.
Notes: Therapies taken during retreatment period in the axicabtagene ciloleucel arm are included.

In Table above, percentages represent subject incidences for each therapy, regardless of lines of therapy that each subject received, and if multiple therapies are included in the line of therapy, each line of therapy can be counted in > 1 category (eg, if salvage chemotherapy followed by high-dose therapy [HDT]+auto-SCT is considered a line of therapy per investigator, it is counted under both chemo[immune]therapy and HDT+auto-SCT).

Overall, 38% of patients received chemo(immuno)therapy as any line of subsequent therapy, while 29% received this therapy as the first subsequent therapy after axicabtagene ciloleucel.

Data collection for subjects who received subsequent therapies was limited and did not include collection of scheduled disease assessments. Subsequent therapies were not protocol-defined and, after new lymphoma therapy, disease assessments were not required at regular intervals (as was for on-protocol therapy) and were per standard of care and investigator discretion.

Therefore, efficacy analyses for the 29% of subjects (n = 53) who received chemo(immuno)therapy as the first subsequent therapy after the axicabtagene ciloleucel infusion are limited to ORR, CR, time-to-next therapy, and the percentage who proceeded to HDT-ASCT (13%; n = 7) and are summarized in Table below. EFS and progression-free survival (PFS) are not provided because there were no scheduled disease assessments after a subject received a new lymphoma therapy, which was received off-protocol, and the date of the last evaluable disease assessment could not be obtained for EFS and PFS censoring.

**Table 13. Subsequent Chemo(immuno)therapy and Transplant in the Axicabtagene Ciloleucel Arm of ZUMA-7 (Full Analysis Set, N = 180)**

| | Axicabtagene Ciloleucel (N = 180) |
|---|---|
| Received chemo(immuno)therapy as first subsequent therapy, n(%)[a] | 53 (29) |
| Best Response to chemo(immuno)therapy, n(%)[b] | |
| Objective responders (CR + PR) | 12 (23) |
| Complete response | 7 (13) |
| Partial response | 5 (9) |
| Stable disease | 8 (15) |
| Progressive disease | 26 (49) |
| Not evaluable | 5 (9) |
| Missing | 2 (4) |
| Median (95% CI) time to next therapy, months | 2.4 (1.8, 2.7) |
| Received HDT and ASCT after chemo(immuno)therapy, n(%)[b] | 7 (13) |
| Received allo-SCT after chemo(immuno)therapy, n(%)[b] | 1 (2) |

Data cutoff date = 18MAR2021.

Abbreviations:allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; HDT, high-dose therapy; PR, partial response.

Notes: Time to next therapy is defined as the time from initiation of chemo(immuno)therapy (as the first subsequent therapy) to the start of the next subsequent lymphoma therapy (not including transplant immediately following chemo(immuno)therapy) or death from any cause. Subjects who did not receive subsequent lymphoma therapy after their chemo(immuno)therapy and were still alive were censored at the last known alive date.

a Percentage is based on the number of subjects in the analysis set.

b Percentages are based on the number of subjects received chemo(immuno)therapy as first subsequent therapy.

**PRO results**

1. EORTC QLQ-C30 Global Health Status

Baseline (screening visit) mean EORTC QLQ-C30 global health status scores for evaluable subjects in the QoL analysis set were comparable between the axicabtagene ciloleucel (68.6 [95% CI: 65.6, 71.7]) and SOCT (70.1 [95% CI: 66.1, 74.1]) arms.

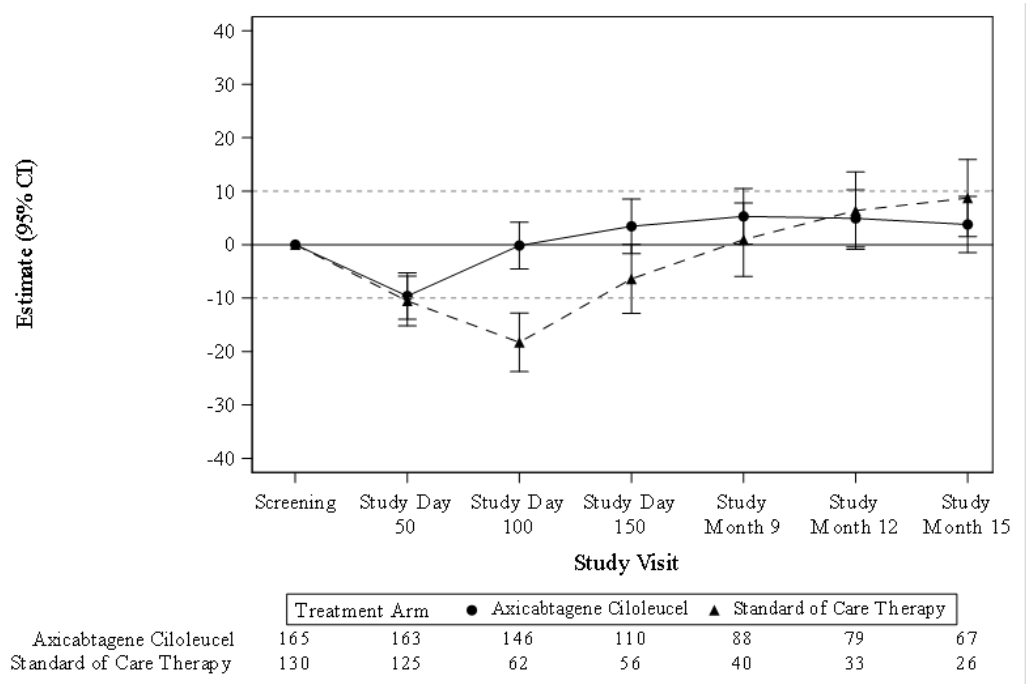
There was a statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 (estimated difference 18.1 [95% CI: 12.3, 23.9]; adjusted $p < 0.0001$) in favor of axicabtagene ciloleucel. This difference was also statistically significant at Study Day 150 (estimated difference 9.8 [95% CI: 2.6, 17.0]; adjusted $p = 0.0124$). Mean estimated scores had numerically returned to or exceeded scores at baseline by Study Day 100 for the axicabtagene ciloleucel arm versus at Month 9 for the SOCT arm.

**Table 14.EORTC QLQ-C30 Global Health Status/QoL Mixed Model with Repeated Measures Difference in Change from Baseline (Screening Visit) (Axicabtagene Ciloleucel – SOCT; QoL Analysis Set)**

| Patient-reported Outcome Score | Visit | Estimate (95% CI) | Unadjusted P-value[a] | Adjusted P-value[a] |
|---|---|---|---|---|
| EORTC QLQ-C30 Global Health Status/QoL | Day 100 | 18.1 (12.3, 23.9) | <.0001 | <.0001 |
| | Day 150 | 9.8 (2.6, 17.0) | 0.0077 | 0.0124 |
| | Month 9 | 4.4 (-3.3, 12.0) | 0.2655 | 0.2655 |
| | Month 12 | -1.5 (-9.6, 6.6) | nd | nd |
| | Month 15 | -4.9 (-13.0, 3.1) | nd | nd |

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; nd, not displayed; QoL, quality of life; SOCT, standard of care therapy.
a P-values are only presented for Study Day 100 and only for subsequent visits when the previous visit was statistically significant ($p < 0.05$). Adjusted p-values were calculated using the False Discovery Rate methodology.

**Figure 13. EORTC QLQ-C30 Global Health Status Score/QoL Mixed Model with Repeated Measures for Change from Baseline (Screening Visit) (QoL Analysis Set)**




Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; IPI, International Prognostic Index; QoL, quality of life.
Notes: Results are populated only through Month 15 due to lack of model convergence when using time points. Horizontal lines represent the minimally important difference thresholds for meaningful change and are provided for clarity of interpretation. This Model included variables for treatment, time, and treatment by time interaction (primary analysis) and controlled for response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≥ 12 months of first-line therapy) and age-adjusted IPI (0 to 1 vs 2 to 3) at time of screening.

2. EORTC QLQ-C30 Physical Functioning

Baseline (screening visit) mean EORTC QLQ-C30 physical functioning scores for evaluable subjects in the QoL analysis set were comparable between the axicabtagene ciloleucel (83.5 [95% CI: 80.8, 86.2]) and SOCT (85.3 [95% CI: 82.0, 88.6]) arms.

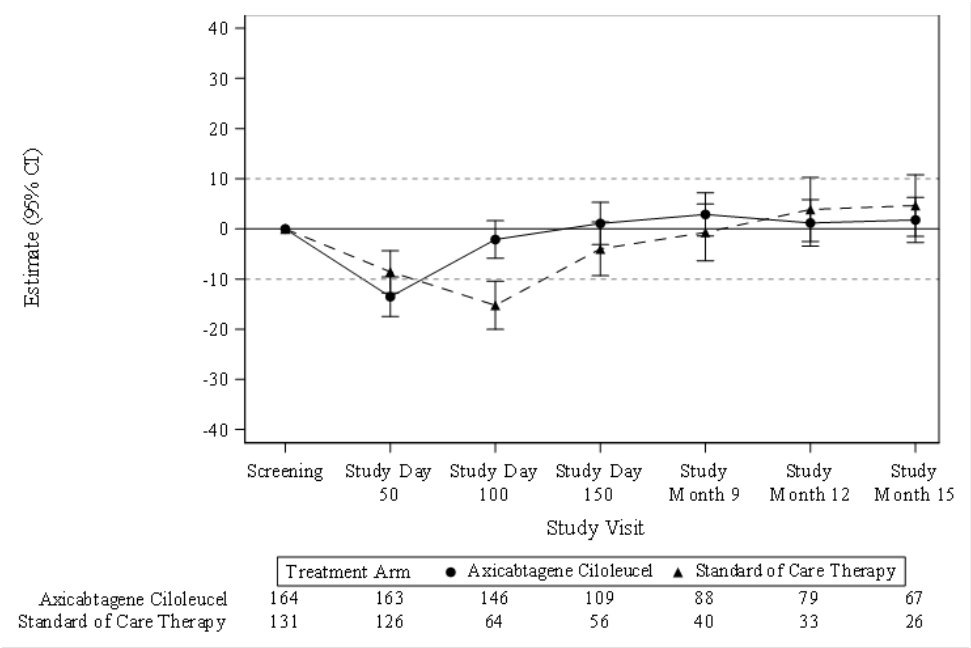
There was a statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 (estimated difference 13.1 [95% CI: 8.0, 18.2]; adjusted $p < 0.0001$) in favor of axicabtagene ciloleucel. Mean estimated scores had numerically returned to or exceeded scores at baseline by Study Day 150 for the axicabtagene ciloleucel arm versus at Month 12 for the SOCT arm.

**Table 15. EORTC QLQ-C30 Physical Functioning Mixed Model with Repeated Measures Difference in Change from Baseline (Screening Visit) (Axicabtagene Ciloleucel – SOCT; QoL Analysis Set)**

| Patient-reported Outcome Score | Visit | Estimate (95% CI) | Unadjusted P-value[a] | Adjusted P-value[a] |
|---|---|---|---|---|
| EORTC QLQ-C30 Physical Functioning | Day 100 | 13.1 (8.0, 18.2) | <.0001 | <.0001 |
| | Day 150 | 5.1 (-0.9, 11.0) | 0.0940 | 0.1253 |
| | Month 9 | 3.6 (-2.7, 9.8) | nd | nd |
| | Month 12 | -2.7 (-9.8, 4.5) | nd | nd |
| | Month 15 | -2.9 (-9.7, 4.0) | nd | nd |

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; nd, not displayed; QoL, quality of life; SOCT, standard of care therapy.
a P-values are only presented for Study Day 100 and only for subsequent visits when the previous visit was statistically significant ($p < 0.05$). Adjusted p-values were calculated using the False Discovery Rate methodology.

**Figure 14. EORTC QLQ-C30 Physical Functioning Mixed Model with Repeated Measures for Change from Baseline (Screening Visit) (QoL Analysis Set)**



Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; IPI, International Prognostic Index; QoL, quality of life.
Notes: Results are populated only through Month 15 due to lack of model convergence when using time points. Horizontal lines represent the minimally important difference thresholds for meaningful change and are provided for clarity of interpretation. This Model included variables for treatment, time, and treatment by time interaction (primary analysis) and controlled for response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≥ 12 months of first-line therapy) and age-adjusted IPI (0 to 1 vs 2 to 3) at time of screening.

3. EQ-5D-5L VAS

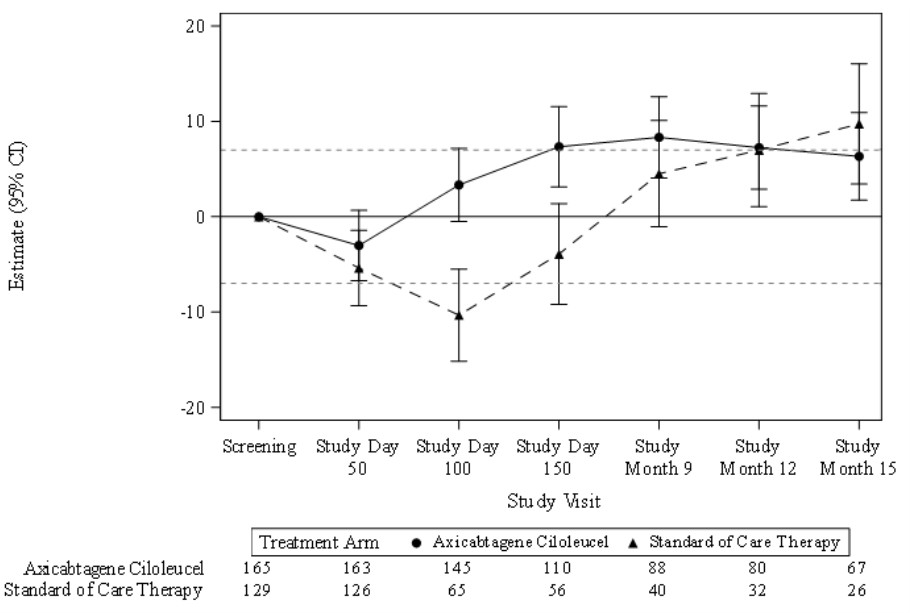
Baseline (screening visit) mean EQ-5D-5L VAS scores were comparable between the axicabtagene ciloleucel (72.4 [95% CI: 69.5, 75.2]) and SOCT (74.4 [95% CI: 70.9, 77.9]) arms.
There was a statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 (estimated difference 13.7 [95% CI: 8.5, 18.8]; adjusted p < 0.0001) and Study Day 150 (estimated difference 11.3 [95% CI: 5.4, 17.1]; adjusted p = 0.0004) in favor of axicabtagene ciloleucel. Mean estimated scores had numerically returned to or exceeded scores at baseline by Study Day 100 for the axicabtagene ciloleucel arm versus Month 9 in the SOCT.

**Table 16. EQ-5D-5L VAS Mixed Model with Repeated Measures Difference in Change from Baseline (Screening Visit) (Axicabtagene Ciloleucel – SOCT; QoL Analysis Set)**

| Patient-reported Outcome Score | Visit | Estimate (95% CI) | Unadjusted P-value[a] | Adjusted P-value[a] |
|---|---|---|---|---|
| EQ-5D-5L VAS | Day 100 | 13.7 (8.5, 18.8) | <.0001 | <.0001 |
| | Day 150 | 11.3 (5.4, 17.1) | 0.0002 | 0.0004 |
| | Month 9 | 3.8 (-2.3, 10.0) | 0.2230 | 0.2549 |
| | Month 12 | 0.3 (-6.3, 6.8) | nd | nd |
| | Month 15 | -3.4 (-10.4, 3.6) | nd | nd |

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life 5-Dimensions 5 Levels; nd, not displayed; QoL, quality of life; SOCT, standard of care therapy; VAS, visual analog scale.
a P-values are only presented for Study Day 100 and only for subsequent visits when the previous visit was statistically significant (p < 0.05). Adjusted p-values were calculated using the False Discovery Rate methodology.

**Figure 15. EQ-5D-5L VAS Mixed Model with Repeated Measures for Change from Baseline (Screening Visit) (QoL Analysis Set)**




Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life 5-Dimensions 5 Levels; IPI, International Prognostic Index; QoL, quality of life; VAS, visual analog scale.
Notes: Results are populated only through Month 15 due to lack of model convergence when using time points. Horizontal lines represent the minimally important difference thresholds for meaningful change and are provided for clarity of interpretation. This Model included variables for treatment, time, and treatment by time interaction (primary analysis) and controlled for response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≥ 12 months of first-line therapy) and age-adjusted IPI (0 to 1 vs 2 to 3) at time of screening.

## *Summary of main study*

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 17. Summary of Efficacy for trial ZUMA-7**

| **Title: A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)** | | |
|---|---|---|
| Study identifier | KTE-C19-107 (EudraCT number: 2017-002261-22) | |
| Design | Phase 3 randomized, open-label, multicenter study. Superiority study comparing efficacy of Axicabtagene Ciloleucel to Standard of Care | |
| | Duration of main phase:<br><br>Duration of Run-in phase:<br>Duration of Extension phase: | First subject enrolled: 25 January 2018, study ongoing<br>not applicable<br>not applicable |
| Hypothesis | Superiority: Axicabtagene ciloleucel will prolong EFS compared to standard of care therapy in adult subjects with relapsed/refractory DLBCL. The hypothesized treatment effect corresponds to a 50% improvement in EFS. | |
| Treatments groups | Axicabtagene Ciloleucel Treatment Arm | Axicabtagene Ciloleucel. Number randomized: 180, number treated: 170 |

| | | | |
|---|---|---|---|
| | SOCT Treatment Arm | | Second-line (salvage) chemotherapy regimen (R-ICE, R-DHAP, R-ESHAP, or RGDP). Subjects responding to salvage chemotherapy after 2 or 3 cycles were to proceed with HDT and auto-SCT. Subjects who did not respond to salvage chemotherapy could have received additional treatment off protocol. Number randomized: 179, number treated (at least 1 dose): 168 |
| Endpoints and definitions | Primary endpoint | EFS | Event Free Survival (EFS): EFS is defined as the time from randomization to the earliest date of disease progression per the Lugano Classification, commencement of new lymphoma therapy, or death from any cause. |
| | Key Secondary endpoints | ORR<br>OS | Objective response rate (ORR): ORR is defined as the incidence of either a complete response or a partial response by the Lugano Classification as determined by blinded central review.<br><br>Overall survival (OS): OS is defined as the time from randomization to death from any cause. |
| | Other Secondary endpoints | mEFS<br>PFS<br>DOR | Modified EFS (mEFS): mEFS is defined the same way as EFS, except that failure to attain CR or PR by Day 150 assessment is not considered as an event.<br>PFS is defined as the time from randomization to disease progression per Lugano Classification as determined by investigator review or death from any cause.<br>DOR is derived only among subjects who experience an objective response per Lugano Classification as determined by blinded central review and is defined as the time from first response to disease progression per the Lugano Classification or death from any cause. |
| Database lock | 18 MAR 2021 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |

| | **Axicabtagene Ciloleucel (N = 180)** | **Standard of Care (N = 179)** |
|---|---|---|
| **Primary Endpoint** | | |
| EFS, by blinded central assessment | | |
| Events, n (%) | 108 (60) | 144 (80) |
| Censored[a], n (%) | 72 (40) | 35 (20) |
| Stratified HR (95% CI), log-rank p-value | 0.398 (0.308, 0.514), < 0.0001 | |
| KM median (95% CI) EFS time (months) | 8.3 (4.5, 15.8) | 2.0 (1.6, 2.8) |
| Min, Max EFS time (months) | 0, 31+ | 0+, 33+ |
| Event-free rate, % (95% CI) by KME | | |
| 12 months | 47.2 (39.8, 54.3) | 17.6 (12.3, 23.6) |
| 24 months | 40.5 (33.2, 47.7) | 16.3 (11.1, 22.2) |
| **Key Secondary Endpoints** | | |

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| ORR, by blinded central assessment | | |
| Objective responders (CR + PR), n (%), (95% CI) | 150 (83), (77.1, 88.5) | 90 (50), (42.7, 57.8) |
| Difference in ORR, % (95% CI), stratified CMH test p-value | 33.1 (23.2, 42.1), < 0.0001 | |
| CR, n (%), (95% CI) | 117 (65), (57.6, 71.9) | 58 (32), (25.6, 39.8) |
| Interim OS | | |
| Death from any cause, n (%) | 72 (40) | 81 (45) |
| Alive, n (%) | 108 (60) | 98 (55) |
| Stratified HR (95% CI), log-rank p-value | 0.730 (0.530, 1.007), 0.027 | |
| KM median (95% CI) OS time (months) | NR (28.3, NE) | 35.1 (18.5, NE) |
| Min, Max OS time (months) | 1, 38+ | 0+, 37+ |
| Survival rate % (95% CI) by KME | | |
| 12 months | 76.0 (69.1, 81.6) | 64.7 (57.0, 71.4) |
| 24 months | 60.7 (52.8, 67.7) | 52.1 (44.0, 59.5) |
| **Additional Secondary Endpoints** | | |
| EFS, by investigator assessment | | |
| Events, n (%) | 103 (57) | 140 (78) |
| Censored, n (%) | 77 (43) | 39 (22) |
| Stratified HR (95% CI) | 0.404 (0.311, 0.525) | |
| KM median EFS time (95% CI) (months) | 10.8 (5.0, 28.6) | 2.3 (1.7, 3.1) |
| Min, Max EFS time (months) | 0, 31+ | 0+, 33+ |
| Event-free rate, % (95% CI) by KME | | |
| 12 months | 49.4 (42.0, 56.5) | 20.1 (14.5, 26.4) |
| 24 months | 43.3 (35.8, 50.5) | 19.5 (13.9, 25.7) |
| PFS, by investigator assessment | | |
| Events, n (%) | 96 (53) | 103 (58) |
| Censored, n (%) | 84 (47) | 76 (42) |
| Stratified HR (95% CI), log-rank p-value | 0.490 (0.368, 0.652), <.0001 | |
| KM median (95% CI) PFS time (months), | 14.7 (5.4, NE) | 3.7 (2.9, 5.3) |
| Min, Max PFS time (months) | 0+, 31+ | 0+, 33+ |
| Event-free rate, % (95% CI) by KME | | |
| 12 months | 52.1 (44.4, 59.2) | 28.2 (20.8, 36.2) |
| 24 months | 45.7 (38.1, 53.0) | 27.4 (20.0, 35.3) |
| DOR, by blinded central assessment | | |
| Number of objective responders (CR + PR) | 150 | 90 |

| | Axicabtagene Ciloleucel (N = 180) | Standard of Care (N = 179) |
|---|---|---|
| Events, n (%) | 66 (44) | 37 (41) |
| Censored, n (%) | 84 (56) | 53 (59) |
| Stratified HR (95% CI), log-rank p-value | 0.736 (0.488, 1.108), 0.0695 | |
| KM median (95% CI) DOR (months) | 26.9 (13.6, NE) | 8.9 (5.7, NE) |
| Min, Max DOR (months) | 0+, 29+ | 0+, 32+ |
| Event-free rate, % (95% CI) by KME | | |
| 12 months | 60.9 (52.4, 68.4) | 47.6 (35.2, 58.9) |
| 24 months | 54.0 (45.1, 62.0) | 45.6 (33.2, 57.1) |
| mEFS, by blinded central assessment | | |
| Events, n (%) | 104 (58) | 144 (80) |
| Censored, n (%) | 76 (42) | 35 (20) |
| Stratified HR (95% CI), log-rank p-value | 0.376 (0.290, 0.487), <.0001 | |
| KM median (95% CI) mEFS time (months) | 10.3 (5.0, 21.5) | 2.0 (1.6, 2.8) |
| Min, Max mEFS time (months) | 0, 31+ | 0+, 33+ |
| Event-free rate, % (95% CI) by KME | | |
| 12 months | 49.4 (42.0, 56.5) | 17.6 (12.3, 23.6) |
| 24 months | 42.7 (35.3, 49.9) | 16.3 (11.1, 22.2) |

## 2.5.2. Discussion on clinical efficacy

## Design and conduct of clinical studies

ZUMA-7 is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus SOCT in adult subjects with r/r LBCL. Adult subjects with r/r LBCL after first-line rituximab and anthracycline-based chemotherapy were randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOCT. Randomization was stratified by response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy, or relapse > 6 and ≤ 12 months of first-line therapy) and sAAIPI (0 to 1, or 2 to 3), as assessed at the time of screening.

The stratification factor for response to first line therapy was modified in the conduct of study with Amendment 4 and was changed from time since initiation of first line therapy to time since initiation or completion of first line therapy. The inclusion factor for response to first line therapy was modified in the same way. This led to an inclusion criterion and a stratification factor, which were not well-defined after Amendment 4. This change was justified by differing definitions of early relapsed disease in the literature and the fact that also subjects with refractory or progressive disease within 12 months after completion of therapy have a poor prognosis. Neither of these two reasons provide a strong or compelling reason to implement such a change in an ongoing, open-label trial, which is hence not endorsed. Upon request the applicant clarified that this broadened definition of early relapsed disease

lead to the inclusion of only 16 additional subjects (4.5% of the total sample size). On the one hand this makes the necessity of broadening the inclusion criterion somewhat questionable, on the other hand it shows that the impact is likely to be minor. This was further substantiated by sensitivity analyses, which were provided upon request. They show that the treatment effect was only marginally impacted. At the same time they all indicate that the treatment benefit for OS and EFS in subjects who relapsed or were refractory after 12 months from initiation of 1L therapy was smaller compared to subjects who relapsed or were refractory before 12 months from initiation of 1L therapy. To substantiate that a treatment benefit for subjects with later relapse/refractory disease is still present additional subgroup analyses were requested.

For subjects in the axicabtagene ciloleucel arm, treatment consisted of lymphodepleting chemotherapy followed by a single intravenous infusion of axicabtagene ciloleucel. Bridging therapy of corticosteroids was allowed prior to lymphodepleting chemotherapy for subjects with high disease burden, at the discretion of the investigator. For subjects in the SOCT arm, treatment consisted of a platinum-based salvage chemotherapy regimen as selected by the treating investigator from several protocol defined options. Subjects who responded to salvage chemotherapy were to proceed to HDT with or without TBI, followed by auto-SCT. The treatment scheme in the SOCT arm is in line with the current ESMO GL, which recommends salvage regimens with rituximab and chemotherapy followed by HDT and ASCT. The salvage chemotherapy regimens used represent current medical practice.

The primary objective was to determine if axicabtagene ciloleucel is superior to SOCT as measured by EFS, as determined by blinded central assessment.

Key secondary objectives were to evaluate the effect of axicabtagene ciloleucel compared with SOCT on ORR (determined by blinded central assessment), OS, PFS (determined by investigator assessment), and DOR and duration of CR among responding subjects (determined by blinded central assessment), and to evaluate the safety and effect of PROs and QoL of axicabtagene ciloleucel compared with SOCT.

The analysis of EFS, ORR and OS was controlled for multiplicity using a hierarchical approach.

The analysis of OS followed a group sequential design (i.e., with interim analyses), which was modified multiple times throughout the study. The first interim analysis was planned at the time the EFS analysis, which was initially assumed to happen after 140 OS events. With Amendment 5 (25 June 2020) this interim analysis was assumed to happen after 110 OS events and a second interim analysis after 160 OS events was introduced. In parallel the alpha-spending function was changed from an O'Brien-Fleming spending function to a Kim-deMets spending function. The changes were justified by the lower number of expected OS events by the time of the EFS analysis and by the wish to reserve sufficient alpha for the final analysis in order to maintain the overall power for OS, which is considered comprehensible. Nominal significance levels were defined in the protocol as well, but did not match the alpha spending function (see Statistical Methods for details). At the time of the first interim analysis (18 March 2021) the second interim analysis was dropped again as 153 events had accrued by that time. Upon request the MAH clarified that the Kim-deMets alpha spending function (with $\rho = 6$) and one interim analysis after 153 OS evens (IF = 73%) and a final analysis planned at 210 events is to be used. This leaves $\alpha = 2.44\%$ for the final analysis. In principle this is considered acceptable. However, given the uncertainties in the definition of the alpha spending function and significance levels to be applied and the post hoc nature of this decision, this is considered to add uncertainties with respect to the robustness of the OS analyses. A type 1 error inflation cannot be fully excluded.

The study was open-label, which is endorsed given the different treatment (and manufacturing) profiles, where blinding would have been infeasible. A DSMB was installed for safety (and efficacy)

reviews and a trial integrity document (TID) was in place to detail the access to (restricted) data, which is in principle endorsed as well.

It can be seen from the TID, however, that not only monitors had access to subject level or aggregated data but that operations managers, statistical programmers and biostatisticians had access, the latter to full access at any time. Seemingly the access to treatment allocation was restricted for all sponsor's personnel, and statisticians involved in the protocol changes were not identical to the study team biostatisticians/programmers and had no access to the ZUMA-7 study data. However, no clearly defined firewall was in place to separate individuals involved in the monitoring of the study from individuals involved in the conduct of the study. This is considered problematic as it cannot be excluded that changes have been made in the light of the accruing data (i.e., post hoc with an unknown and unquantifiable impact on the results especially for OS). Upon request, the MAH clarified that no analyses by treatment arm were conducted prior to the primary EFS analysis and that the decisions were not made in the light of accruing data.

A total of 359 subjects were randomly assigned in a 1:1 ratio to receive axicabtagene ciloleucel or SOCT, with 180 subjects in the axicabtagene ciloleucel arm and 179 subjects in the SOCT arm.

In the axicabtagene ciloleucel arm 178 patients underwent leukapheresis, 65 patients received bridging therapy, 172 patients received lymphodepleting chemotherapy, and 170 patients received axicabtagene ciloleucel.

While more male and younger subjects were enrolled, the distribution across the two treatment arms are similar. The distribution of patients across baseline and disease characteristics was similar in both arms. While the distribution between the two treatment arms is similar here as well, the molecular subgrouping seems to be slightly different compared to the general DLBCL population: 61% GCB and 9% ABC (55%-5% in the SOCT arm), whereas in the literature there is a prevalence of 50% vs ~35-40% for these subtypes. This means a relative underrepresentation of the ABC subtype, although this is similarly present in both treatment arms.

For the 180 subjects in the axicabtagene ciloleucel arm and the 179 subjects in the SOCT arm, the median potential follow-up time was 25.00 months (range: 17.48 to 37.75 months) and 24.84 months (range: 17.58 to 37.26 months), respectively; and the median actual follow-up time was 20.07 months (range: 0.59 to 37.75 months) and 18.23 months (range: 0.03 to 37.26 months), respectively.

## Efficacy data and additional analyses

The primary objective of the study was met: at the primary EFS analysis, axicabtagene ciloleucel treatment resulted in a statistically significant reduction in the risk of an EFS event compared with SOCT (stratified HR = 0.398 [95% CI: 0.308, 0.514]; stratified log-rank $p < 0.0001$).

These EFS data provide compelling arguments in favour of axicabtagene ciloleucel in the patient population studied. Importantly, there seem to be no difference in efficacy for sex, and also both age groups below and above 65 years benefitted from the therapy.

Of note, EFS events were imputed as the randomization date (in case of the initiation of a new lymphoma therapy in the absence of any evaluable disease assessment). Given the nature of the events that led to an imputation for an EFS event at Day 0 (in cases where a patients' preference for another treatment than the assigned standard of care) and the imbalances in these events between treatment groups (N = 10 in SOCT and N = 2 in axicabtagene ciloleucel) this is considered problematic. It seems to be partly

based on patients' preferences in this open label study and results in bias in favor of axicabtagene ciloleucel. This apparently makes the derived treatment estimates for EFS anti-conservative. Despite the definition in the SAP this is hence not endorsed. It is acknowledged, however, that these intercurrent events do not impact the derivation and interpretation of OS, and should not impact EFS to an extend which would render the benefit questionable.

Importantly, there is no difference in the EFS results for the different molecular subtypes, and axicabtagene ciloleucel treatment provided a benefit for both GCB-like and ABC-like disease: generally, ABC DLBCL is associated with substantially worse outcomes when treated with standard chemoimmunotherapy. Additionally, axicabtagene ciloleucel proved to be superior to SOCT for all disease subtypes.

While for EFS (per central assessment), axicabtagene ciloleucel treatment was superior to SOCT when assessed by CD19 IHC-positive status, for CD19 IHC-negative subjects (number of subjects: n=13 axicabtagene ciloleucel, n=12 SOCT), the KM median EFS was longer in the SOCT arm compared with the axicabtagene ciloleucel arm. Nonetheless, for the ORR (per central assessment), axicabtagene ciloleucel treatment was superior to SOCT when assessed by CD19 IHC-positive or IHC-negative status. The ORR for CD19 IHC-positive subjects in the axicabtagene ciloleucel and SOCT arms was 83% and 52%, respectively, and for CD19 IHC-negative subjects was 85% and 67%, respectively. However, the complete response data does not show a superiority of axicabtagene ciloleucel treatment: 38% axicabtagene ciloleucel vs. 42% SOCT. It seems that the CD19 negative patients were more likely to have partial response as an outcome when compared to SOCT: 46% vs. 25%.

While similar ORR findings, when comparing the outcomes of CD19 positive vs. negative patients, CD19 positive patients benefitted more from axicabtagene ciloleucel treatment, than the CD19 negative subjects: complete response: 67% for CD19 positives vs. 38% for CD19 negatives; partial response: 16% CD19 positives, 46% CD19 negatives.

While there are a number of CD19 negative patients who benefitted from axicabtagene ciloleucel therapy, a clear-cut and definite superiority of axicabtagene ciloleucel vs. SOCT cannot be established, moreover, outcome data are more favourable in CD19 positive patients when compared to CD19 negative subjects. The data are less reliable due to the lower patient numbers, yet these tendencies are clearly observable. More data are required to draw definite conclusions on the efficacy in CD19 negative patients.

Since there is no definite data to prove a benefit of axicabtagene ciloleucel over SOCT in CD19- negative patients, this aspect needs to be included in the SmPC.

A total of 65 patients (36%) received bridging therapy. In the axicabtagene ciloleucel arm, the ORR was the same for the 65 subjects who received bridging therapy (83%) and the 115 subjects who did not receive bridging therapy (83%) The CR rate was also similar: 66% for subjects who received bridging therapy and 64% for subjects who did not receive bridging therapy. It can be concluded, that bridging therapy did not influence the outcomes measured.

Axicabtagene ciloleucel also demonstrated a statistically significant improvement in ORR with ORR rates of 83% in the axicabtagene ciloleucel arm and 50% in the SOCT arm. Given that objective response is a prerequisite to reach HDT-auto-SCT, the ORR translates into at least 50% of subjects in the SOCT arm not being able to reach definitive therapy. The CR rate was 2-fold higher in the axicabtagene ciloleucel arm (65%) compared with the SOCT arm (32%).

The ZUMA-7 interim OS results (cutoff date 18 Mar 2021) suggested a trend favouring axicabtagene ciloleucel (median OS had not been reached) over SOCT (median OS of 25.7 months). While the data are still immature, the interim analysis of OS favoured axicabtagene ciloleucel over SOCT.

The KM median PFS time was longer in the axicabtagene ciloleucel arm. Although not included in this AR, the PFS subgroup analysis revealed that patients with diagnosis labelled as "other", as well as Asians and African Americans had no benefit beyond standard of care. The importance of this result is blurred by the relatively low number of patients in these subgroups.

### 2.5.3. Conclusions on the clinical efficacy

ZUMA-7 demonstrated superior efficacy of axicabtagene ciloleucel as a second-line therapy in adult subjects with r/r LBCL compared to SOCT. The chosen SOCT arm is in line with the current ESMO GL and, as such, acceptable. Of note, the recruited patient population may not be fully representative of the population encountered in clinical practice (e.g. proportion of ABC-like disease type). Issues in the conduct of study result in uncertainties regarding the derived effects: Measures such as a firewall to fully blind the study team in charge with the conduct of study where not in place and hence decisions to alter the study might have been made in the light of the accrued data. Modifications to the analysis plan for OS render the type 1 error control for OS questionable. As the study was not powered for OS, only a numerical (rather than statistically significant) benefit might be derived for OS anyhow. Given the results for EFS, ORR and CR, this is considered acceptable.

## *2.6. Clinical safety*

### *Introduction*

The safety data analysis set (SAS) is based on the main study KTE-C19-107 (ZUMA 7), which is an ongoing (FU ongoing, not recruiting) Phase 3 randomized open label clinical trial in adult subjects with relapsed/refractory DLBCL, evaluating axicabtagene ciloleucel compared with SOCT (salvage chemotherapy followed by HDT-auto-SCT) as second line treatment. The primary analysis was performed when 250 event-free survival (EFS) events had been observed by central assessment and all subjects had passed the Month 9 time point. Data are provided as of DCO 18 Mar 2021 for 170 subjects who received axicabtagene ciloleucel and 168 subjects who received at least 1 dose of salvage chemotherapy in the SOCT arm (safety analysis set).

At the date of data cutoff (18 March 2021), the ZUMA-7 study had ended for 66 subjects (37%) who had received axicabtagene ciloleucel and for 86 subjects (48%) who had received ≥ 1 dose of standard of care salvage chemotherapy. The primary reason for ending the study for subjects who received axicabtagene ciloleucel was death for 64 subjects (36%) and lost to follow-up for 2 subjects (1%). The primary reason for ending the study for subjects who received SOCT was death for 75 subjects (42%), withdrawal of consent for 7 subjects (4%), lost to follow-up for 2 subjects (1%), investigator decision for 1 subject (1%), and other reason for 1 subject (1%). At DCO, the median actual follow-up times of subjects in the axicabtagene ciloleucel and SOCT arms were 19.6 months and 18.0 months, respectively; the median potential follow-up times were 24.1 months and 24.9 months, respectively, and the minimum potential follow-up times were 16.0 months and 17.2 months, respectively.

ZUMA7 Key Dates (source Summary Clinical Safety)

| Event | Date |
|---|---|

| | |
|---|---|
| First subject screened | 22 January 2018 |
| First subject randomized (ie, enrolled) | 25 January 2018 |
| Last subject randomized (ie, enrolled) | 04 October 2019 |
| Subjects enrolled: n=359<br>(n= 180 randomized in axicabtagene ciloleucel arm; n= 179 randomized in SOCT arm) | |
| Data cutoff date | 18 March 2021 |
| Treatment unblinding | 18 June 2021 |
| Subjects enrolled: n=359<br>(n= 180 randomized in axicabtagene ciloleucel arm; n= 179 randomized in SOCT arm) | |
| Subjects, who received axicabtagene ciloleucel: n=170<br>Subjects who received SOCT: n=168 | |
| Subjects who did not receive lymphodepletion/did not receive axicabtagene ciloleucel: n=6 (2 due to AEs, 2 due to deaths, 1 due to PD, 1 due to "other reason")<br>Subjects, who received lymphodepletion, but did not receive axicabtagene ciloleucel: n=2 (1 due to AE grade 3 stroke and grade 5 ARD, 1 due to Grade 2 intestinal perforation) | b) |

As supportive safety data for this indication extension application, the MAH submitted results from the ongoing (FU ongoing, not recruiting) KTE-C19-101 (ZUMA-1) study, Phase 1 and Phase 2 Cohorts 1 and 2. The ZUMA-1 study title is "A Phase1/2 Multicenter Study Evaluation the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive non-Hodgkin-Lymphoma". Data are included and presented side by side and pooled with the 18 Mar 2021 as date of DCO for the analyses. The median actual follow-up time were 23.5 months, and the minimum of potential follow-up time was 54.1 months. At DCO the study had ended for 63 subjects (53%) who had received axicabtagene ciloleucel. For all 63 subjects whose participation in the study has ended, the primary reason was death.

Study Synopses

| | Type of Study | Study Number | Study Objectives | Design | Study and Control Drug Regimens | Duration of Treatment | Number of Subjects | Study Population/ Entry Criteria | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| | Phase 3 | KTE-C17-107 (ZUMA-7) | Evaluate the efficacy and safety of axicabtagene ciloleucel versus SOCT in subjects with r/r LBCL. | Randomized, controlled, open-label; safety and efficacy; multicenter. | Axicabtagene ciloleucel arm:<br>Lymphodepleting chemotherapy regimen consisting of fludarabine 30 mg/m$^2$/day and cyclophosphamide 500 mg/m$^2$/day for 3 days, followed by 2 rest days prior to a single infusion of axicabtagene ciloleucel:<br>2 x 10$^6$ anti-CD19 CAR T cells/kg.<br><br>SOCT arm:<br>Protocol-defined salvage chemotherapy regimen (R-ICE, R-DHAP/R-DHAX, R-ESHAP, or R-GDP) as selected by the treating investigator, administered every 2 to 3 weeks for 2 to 3 cycles. Subjects responding to salvage chemotherapy after 2 or | Axicabtagene ciloleucel arm:<br>Single infusion of axicabtagene ciloleucel.<br><br>SOCT arm:<br>2 to 3 cycles of platinum-based salvage chemotherapy administered every 2 to 3 weeks. Responders were to proceed with HDT auto-SCT per institutional standards and nonresponders could receive additional | Planned:<br>Approximately 350 subjects randomized 1:1 to 1 of 2 treatment arms.<br><br>Full Analysis Set:<br>359 subjects; 180 subjects randomized to the axicabtagene ciloleucel arm and 179 subjects randomized to the SOCT arm. | Relapsed or refractory LBCL after first-line rituximab and anthracycline-based chemotherapy (adults). | Follow-up ongoing, not recruiting; Primary Analysis CSR (m5.3.5.1) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 3 cycles were to proceed with HDT-auto-SCT per institutional or regional standards. Subjects not responding to salvage chemotherapy could receive additional treatment off protocol. | treatment off protocol. | | | |
| | Phase 1/2 | KTE-C19-101 (ZUMA-1) | Evaluate the safety and efficacy of axicabtagene ciloleucel in adult subjects with refractory LBCL, including DLBCL NOS, PMBCL, and TFL, after ≥ 2 lines of systemic therapy. | Single-arm, open-label; safety and efficacy; multicenter | Lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m$^2$/day and fludarabine 30 mg/m$^2$/day for 3 days followed by axicabtagene ciloleucel infusion: 2 x 10$^6$ anti-CD 19 CAR T cells/kg. | Single infusion of axicabtagene ciloleucel | Planned Phase 1 approximately 6 to 24 subjects<br>Planned Phase 2 approximately 92 subjects<br>Phase 1<br>8 leukapheresed; 7 treated<br>Phase 2 Pivotal<br>111 leukapheresed; 101 treated<br>*Enrollment complete* | Relapsed or refractory LBCL, including DLBCL NOS, PMBCL, and TFL after 2 or more lines of systemic therapy (adults)<br>Phase 1<br>Refractory DLBCL, PMBCL, or TFL<br>Phase 2 Pivotal<br>Cohort 1: refractory DLBCL<br>Cohort 2: refractory PMBCL or TFL | Follow-up ongoing, not recruiting;<br>ISS (m2.7.4) |

- Axicabtagene ciloleucel was used as 2$^{nd}$-line-treatment in ZUMA-7, while subjects in ZUMA-1 had previously received 2 or more lines of systemic chemotherapy

## *Patient exposure*

KTE-C19-107 (ZUMA-7), Main Study

*Exposure to lymphodepletion (cyclophosphamide and fludarabine)*

Of 170 subjects, 169 had an available BSA (body surface area). Median BSA cyclophosphamide adjusted dose was 1,500 mg/m$^2$ (range: 1,211 to 1,618 mg/m$^2$), and median BSA fludarabine adjusted dose was 90mg/m$^2$ (range 60 to 95 mg/m$^2$. A total of 165/169 (98%) and 164/165 (97%) subjects received the planned total BSA-adjusted dose (± 10%) of cyclophosphamide (1,500 mg/m2) and fludarabine (90 mg/m2), respectively.

**Table 18. Exposure to Lymphodepleting Chemotherapy (Safety Analysis Set – Axicabtagene Ciloleucel Arm); source Report Body**

| Axicabtagene Ciloleucel (N = 170) | |
|---|---|
| Cyclophosphamide | |
| Total BSA adjusted dose (mg/m$^2$)[a] | |
| n[b] | 169 |
| Mean (STDEV) | 1483.2 (51.1) |
| Median (Q1, Q3) | 1500.0 (1475.7, 1500.0) |
| Min, Max | 1211, 1618 |
| Subjects received +/- 10% planned total dose, n (%) | 165 (97) |
| Fludarabine | |
| Total BSA adjusted dose (mg/m$^2$)[a] | |
| n[b] | 169 |
| Mean (STDEV) | 88.9 (4.1) |
| Median (Q1, Q3) | 90.0 (88.8, 90.0) |
| Min, Max | 60, 96 |
| Subjects received +/- 10% planned total dose, n (%) | 164 (96) |

*Exposure to axicabtagene ciloleucel*

Axicabtagene ciloleucel was infused in an inpatient setting, where subjects were monitored at a healthcare facility for a minimum of 7 days. Five subjects/170 (3%) were planned as outpatient infusion with subsequent elective submission to a hospital for observation. All 170 treated subjects were eventually hospitalized with a median duration of hospitalization of 16 days (range: 5 to 103 days). For all 170 subjects in the axicabtagene ciloleucel arm of the safety analysis set, the median total number of anti-CD19 CAR T cells in the axicabtagene ciloleucel infusion was 170 × 10$^6$ cells (range: 58 to 200 × 10$^6$ cells) and the median total number of T cells infused was 301.5 × 10$^6$ (range: 88 to 633 × 10$^6$ cells). 166/170 subjects (98%) received within 10% of the planned dose of 2 × 10$^6$ anti-CD19 CAR T cells/kg (or a flat dose of 200 × 10$^6$ anti-CD19 CAR T cells for subjects weighing > 100 kg). For the 137 subjects who received axicabtagene ciloleucel and weighed ≤ 100 kg (81%), the median weight-adjusted dose

was 2 × $10^6$ anti-CD19 CAR T cells/kg (range: 1.0 to 2.1 × $10^6$ cells/kg) and all 33 subjects who weighed > 100 kg (19%) received the planned flat total dose of 200 × $10^6$ anti-CD19 CAR T cells.

**Table 19. Exposure to Axicabtagene Ciloleucel (Safety Analysis Set – Axicabtagene Ciloleucel Arm)**

| | Axicabtagene Ciloleucel (N = 170) |
|---|---|
| Axicabtagene ciloleucel | |
| Weight-adjusted dose received ($10^6$ CAR T cell/kg) for subjects with weight ≤ 100kg | |
| n | 137 |
| Mean (STDEV) | 1.98 (0.14) |
| Median (Q1, Q3) | 2.00 (2.00, 2.00) |
| Min, Max | 1.0, 2.1 |
| Total dose received ($10^6$ CAR T cells) for subjects with weight > 100kg | |
| n | 33 |
| Mean (STDEV) | 200.0 (0) |
| Median (Q1, Q3) | 200.0 (200.0, 200.0) |
| Min, Max | 200, 200 |
| Total number of CAR T cells (x$10^6$) | |
| n | 170 |
| Mean (STDEV) | 161.6 (33.2) |
| Median (Q1, Q3) | 170.0 (140.0, 190.0) |
| Min, Max | 58, 200 |
| Total number of T cells infused (x$10^6$) | |
| n | 170 |
| Mean (STDEV) | 308.4 (90.7) |
| Median (Q1, Q3) | 301.5 (242.9, 363.6) |
| Min, Max | 88, 633 |
| Subjects received +/- 10% planned total dose[a], n (%) | 166 (98) |

*Exposure to SOCT*

For the 168 subjects in the SOCT arm of the safety analysis set, 152 subjects (90%) received 2 or 3 cycles as directed by the protocol, as outlined below, and 16 subjects (10%) received 1 cycle of salvage chemotherapy. Among the subjects who received 2 or 3 cycles of salvage chemotherapy and responded, defined by CR or PR per investigator assessment at Study Day 50, 64 subjects received HDT and reached HDT-auto-SCT, of whom 62 subjects (37% of the SOCT – safety analysis set) went on to receive auto-SCT on protocol and 2 subjects received auto-SCT off protocol. In the SOCT arm, there were 59 incidences of hospitalization for administration of SCT and the median duration of hospitalization was 21 days (range: 1 to 3 days).

**Table 20. Exposure to SOCT (Safety Analysis Set – SOCT Arm)**

| | Standard of Care (N = 168) n (%) |
|---|---|
| Subjects received any standard of care second-line salvage chemotherapy | 168 (100) |
| Number of cycles received | |
| 1 cycle | 16 (10) |
| 2 cycles | 91 (54) |
| 3 cycles | 61 (36) |
| Number of subjects responded with CR/PR but did not receive HDT-ASCT[a] | 3 (2) |
| Number of subjects responded with CR/PR and received HDT-ASCT | 62 (37) |
| After 2 cycles | 20 (12) |
| After 3 cycles | 42 (25) |
| Rituximab + Ifosfamide, Carboplatin, and Etoposide (R-ICE) | 84 (50) |
| Number of cycles received | |
| 1 cycle | 8 (5) |
| 2 cycles | 47 (28) |
| 3 cycles | 29 (17) |
| Number of subjects responded with CR/PR but did not receive HDT-ASCT[a] | 2 (1) |
| Number of subjects responded with CR/PR and received HDT-ASCT | 35 (21) |
| After 2 cycles | 13 (8) |
| After 3 cycles | 22 (13) |

| | |
|---|---|
| Rituximab + Etoposide, Methylprednisolone, Cytarabine, and Cisplatin (R-ESHAP) | 5 (3) |
| Number of cycles received | |
| 1 cycle | 1 (1) |
| 2 cycles | 1 (1) |
| 3 cycles | 3 (2) |
| Number of subjects responded with CR/PR but did not receive HDT-ASCT[a] | 0 (0) |
| Number of subjects responded with CR/PR and received HDT-ASCT | 2 (1) |
| After 3 cycles | 2 (1) |
| Rituximab + Gemcitabine, Dexamethasone, and Cisplatin/Carboplatin (R-GDP) | 42 (25) |
| Number of cycles received | |
| 1 cycle | 4 (2) |
| 2 cycles | 20 (12) |
| 3 cycles | 18 (11) |
| Number of subjects responded with CR/PR but did not receive HDT-ASCT[a] | 1 (1) |
| Number of subjects responded with CR/PR and received HDT-ASCT | 15 (9) |
| After 2 cycles | 5 (3) |
| After 3 cycles | 10 (6) |
| Rituximab + Dexamethasone, High-dose Cytarabine and Cisplatin/Oxaliplatin (R-DHAP/R-DHAX) | 37 (22) |
| Number of cycles received | |
| 1 cycle | 3 (2) |
| 2 cycles | 23 (14) |
| 3 cycles | 11 (7) |
| Number of subjects responded with CR/PR but did not receive HDT-ASCT[a] | 0 (0) |
| Number of subjects responded with CR/PR and received HDT-ASCT | 10 (6) |
| After 2 cycles | 2 (1) |
| After 3 cycles | 8 (5) |

## *Adverse events*

Methodology of assessed parameters

*ZUMA-7*

**Adverse events (AEs) and serious AEs (SAEs)** were to be collected from the time of randomization through to either Day 150 after randomization or the initiation of new lymphoma therapy, whichever came first. After Day 150, only targeted SAEs were to be reported. Targeted SAEs are those SAEs that are neurologic, hematologic, infections, autoimmune disorders, and secondary malignancies, and these are to be reported for up to 15 years or 5 years for the axicabtagene ciloleucel and SOCT arms, respectively, or until disease progression, whichever occurs first. All subjects are also followed for survival data for 5 years. All AEs reported were treatment-emergent, defined as having onset date on or after the axicabtagene ciloleucel infusion or on or after the first dose of standard of care-salvage chemotherapy, and were coded according to MedRA V23.1. Because AEs in the original submission for

ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 were coded using MedDRA version 19.0, recoding to MedDRA version 23.1 was performed for terms that had changed between versions 19.0 and 23.1. TEAE subgroups were:

- Age: ≥ 18 years and < 65, or ≥ 65 years
- Sex: male or female
- ECOG performance status at baseline: 0 or 1
- Transduction rate of the CAR T-cell product: by quartiles (axicabtagene ciloleucel-treated subjects only)
- Total number of CAR T cells in the CAR T-cell product: by quartiles (axicabtagene ciloleucel-treated subjects only).

**TEAEs of special interest with axicabtagene ciloleucel** include *identified risks* (CRS, neurologic events, cytopenias, infections, hypogammaglobulinemia), *potential risks* (TLS, secondary malignancies, aggravation of GvHD, immunogenicity, RCR) and *additional risks* (cardiac arrhythmias/failure, autoimmune disorders, bone marrow failure). Prolonged cytopenias were identified as cytopenias present on Day 0 (day of axicabtagene infusion or SOCT first application) or Day 30 after treatment. Aggravation of GvHD was to comprise events that were of new onset or had worsened by 1 or more CTCAE grades after baseline.

**Deaths** were analyzed according to time to death relative to either the axicabtagene ciloleucel infusion or the commencement of standard of care salvage chemotherapy (within 30 days, between 31 and 92 days, or after 92 days).

**Physical examinations, vital signs, and electrocardiograms (ECGs)** were to be assessed at screening and thereafter at regular intervals for up to 24 months and up to 150 days after randomization, respectively. ECGs were to be recorded at baseline and then as clinically indicated.

**Neurological assessments** were to be performed at baseline, and on Day 50 after randomization. In addition, subjects in the axicabtagene ciloleucel arm had neurologic assessments on the day of the axicabtagene ciloleucel infusion and every other day during the 7-day period of hospitalization immediately following the infusion.

**Hematology and blood chemistry:** Samples were to be taken at screening, at regular intervals while the subject's study treatments were ongoing, and at regular intervals thereafter up to Day 150 after randomization. Regular blood samples for hematology will continue to be drawn up to Month 24 after randomization.

**Immunogenicity (axicabtagene ciloleucel arm only)**. Serum samples obtained from subjects prior to leukapheresis and at Day 50 after randomization were to be tested for the development of serum antibodies reactive to the anti-CD19 CAR. If either the pretreatment or Day 50 samples tested positive, further samples were to be taken every 3 months until the subject was either antibody negative or 12 months had passed since the axicabtagene ciloleucel infusion.

**Replication-competent retrovirus (RCR; axicabtagene ciloleucel arm only).** Blood samples obtained from subjects prior to treatment and at Day 150 and Month 12 after randomization were to be tested for the presence of RCR. Additional blood samples are to be collected yearly for up to 15 years and will be tested if a subject tests positive at Day 150 or Month 12 after randomization.

*ZUMA-1(supportive data)*

In general the safety assessments performed were the same, although the timing of some assessments differed. Thus, the difference in safety follow-up between ZUMA-1 and ZUMA-7 is the duration of the collection period for AEs and SAEs. In ZUMA-1, AEs were to be collected from commencement of

leukapheresis, and SAEs were to be collected from the time of informed consent. AE and SAE collection were to continue until Month 3 after the axicabtagene ciloleucel infusion. From Month 3 to either Month 24 or PD (whichever occurred first), only serious targeted AEs were to be reported. To investigate the potential impact of the differences in the duration of safety follow-up for subjects who received axicabtagene ciloleucel in ZUMA-7 and ZUMA-1, ad-hoc analyses of the overall subject incidences of TEAEs and targeted SAEs according to the TEAE or SAE start date were conducted as follows:

- TEAE start date: ≤ 3 months (≤ 92 days) or > 3 months (> 92 days) after the axicabtagene ciloleucel infusion or the first dose of standard of care salvage chemotherapy.

- SAE start date: ≤ 24 months (≤ 731 days) and > 24 months (> 731 days) after the axicabtagene ciloleucel infusion or the first dose of standard of care salvage chemotherapy.

ZUMA-7 Results

*TEAEs*

Of 170 subjects treated with **axicabtagene ciloleucel** in ZUMA-7, all subjects (100%) had ≥ 1 TEAE; 155 subjects (91%) had a worst Grade 3 or higher TEAE. A total of 163 subjects (96%) had ≥ 1 TEAE related to axicabtagene ciloleucel, 112 subjects (66%) had ≥ 1 TEAE related to axicabtagene ciloleucel that was worst Grade 3 or higher, and 63 subjects (37%) had ≥ 1 SAE related to axicabtagene ciloleucel. A total of 14 subjects (8%) experienced Grade 5 TEAEs of whom 7 subjects (4%) had Grade 5 TEAEs that were not PD and 1 subject (1%) had a Grade 5 TEAE (hepatitis B reactivation) considered related to axicabtagene ciloleucel.

Of 168 subjects treated with **SOCT**, all subjects (100%) had ≥ 1 TEAE; 140 subjects (83%) had a worst Grade 3 or higher TEAE. A total of 160 subjects (95%) had ≥ 1 TEAE related to SOCT, 131 subjects (78%) had ≥ 1 treatment-related TEAE that was worst Grade 3 or higher. A total of 7 subjects (4%) experienced Grade 5 TEAEs of whom 2 subjects (1%) had Grade 5 TEAEs that were not PD; both of these Grade 5 treatment-related TEAEs (acute respiratory distress and cardiac arrest) were deemed related to SOCT (specifically HDT).

**Table 21. Overall Summary of TEAEs (Safety Analysis Set); source m5.3.5.1 Report Body**

| | Axicabtagene Ciloleucel (N = 170) n (%) | Standard of Care (N = 168) n (%) |
|---|---|---|
| Any TEAE | 170 (100) | 168 (100) |
| Worst Grade ≥ 3 | 155 (91) | 140 (83) |
| Worst Grade 5 | 14 (8) | 7 (4) |
| Worst Grade 5, excluding PD | 7 (4) | 2 (1) |
| Any serious TEAE | 85 (50) | 77 (46) |
| Worst Grade ≥ 3 | 72 (42) | 67 (40) |
| Worst Grade 5 | 14 (8) | 6 (4)[a] |
| Worst Grade 5, excluding PD | 7 (4) | 2 (1) |
| Any treatment-related TEAE | 163 (96) | 160 (95) |
| Worst Grade ≥ 3 | 112 (66) | 131 (78) |
| Worst Grade 5 | 1 (1) | 2 (1) |
| Worst Grade 5, excluding PD | 1 (1)[b] | 2 (1) |

| | | |
|---|---|---|
| Any serious treatment-related TEAE | 63 (37) | 59 (35) |
| Worst Grade ≥ 3 | 49 (29) | 51 (30) |
| Worst Grade 5 | 1 (1) | 2 (1) |
| Worst Grade 5, excluding PD | 1 (1) | 2 (1) |
| Any TE neurologic event | 102 (60) | 33 (20) |
| Worst Grade ≥ 3 | 36 (21) | 1 (1) |
| Any serious TE neurologic event | 34 (20) | 1 (1) |
| Worst Grade ≥ 3 | 26 (15) | 0 (0) |
| Any TE CRS | 157 (92) | NA |
| Worst Grade ≥ 3 | 11 (6) | NA |
| Any serious TE CRS | 29 (17) | NA |
| Worst Grade ≥ 3 | 10 (6) | NA |
| Any TE hypogammaglobulinemia | 19 (11) | 1 (1) |
| Worst Grade ≥ 3 | 0 (0) | 0 (0) |
| Any TE cytopenias | 136 (80) | 135 (80) |
| Worst Grade ≥ 3 | 128 (75) | 126 (75) |
| Any TE infections | 70 (41) | 51 (30) |
| Worst Grade ≥ 3 | 24 (14) | 19 (11) |
| Worst Grade 5 | 5 (3) | 0 (0) |

TEAEs by System Organ Class:

The 3 most common system organ classes in which TEAEs were reported by treatment arm were as follows:

- Axicabtagene ciloleucel arm: General conditions and administration site conditions (160 subjects, 94%), gastrointestinal disorders (132 subjects, 78%), and nervous system disorders (128 subjects, 75%)
- SOCT arm: Gastrointestinal disorders (143 subjects, 85%), general conditions and administration site conditions (125 subjects, 74%), and blood and lymphatic system disorders (122 subjects, 73%).

**Table 22. Incidence of TEAEs Occurring in ≥ 10% of Subjects in Either Treatment Arm by PT and Worst Grade (Safety Analysis Set)**;

| **Preferred Term<br>Worst CTCAE Grade** | **Axicabtagene Ciloleucel<br>(N = 170)<br>n (%)** | **Standard of Care<br>(N = 168)<br>n (%)** |
|---|---|---|
| Subjects with any TEAE | 170 (100) | 168 (100) |
| Grade 1 | 4 (2) | 8 (5) |
| Grade 2 | 11 (6) | 20 (12) |
| Grade 3 | 33 (19) | 36 (21) |
| Grade 4 | 108 (64) | 97 (58) |
| Grade 5 | 14 (8) | 7 (4) |

| | | |
|---|---|---|
| Grade >= 3 | 155 (91) | 140 (83) |
| Pyrexia | 158 (93) | 43 (26) |
| Grade >= 3 | 15 (9) | 1 (1) |
| Nausea | 69 (41) | 116 (69) |
| Grade >= 3 | 3 (2) | 9 (5) |
| Anaemia | 71 (42) | 91 (54) |
| Grade >= 3 | 51 (30) | 65 (39) |
| Fatigue | 71 (42) | 87 (52) |
| Grade >= 3 | 11 (6) | 4 (2) |
| Diarrhoea | 71 (42) | 66 (39) |
| Grade >= 3 | 4 (2) | 7 (4) |
| Headache | 70 (41) | 43 (26) |
| Grade >= 3 | 5 (3) | 2 (1) |
| Neutropenia | 75 (44) | 29 (17) |
| Grade >= 3 | 73 (43) | 28 (17) |
| Hypotension | 75 (44) | 25 (15) |
| Grade >= 3 | 19 (11) | 5 (3) |
| Neutrophil count decreased | 52 (31) | 47 (28) |
| Grade >= 3 | 49 (29) | 47 (28) |
| Platelet count decreased | 30 (18) | 64 (38) |
| Grade >= 3 | 12 (7) | 60 (36) |
| Hypokalaemia | 44 (26) | 49 (29) |
| Grade >= 3 | 10 (6) | 11 (7) |
| Constipation | 34 (20) | 58 (35) |
| Grade >= 3 | 0 (0) | 0 (0) |
| Vomiting | 33 (19) | 55 (33) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Decreased appetite | 42 (25) | 42 (25) |
| Grade >= 3 | 7 (4) | 6 (4) |
| White blood cell count decreased | 46 (27) | 37 (22) |
| Grade >= 3 | 43 (25) | 31 (18) |
| Sinus tachycardia | 58 (34) | 17 (10) |
| Grade >= 3 | 3 (2) | 1 (1) |
| Hypophosphataemia | 45 (26) | 29 (17) |
| Grade >= 3 | 31 (18) | 21 (13) |
| Thrombocytopenia | 22 (13) | 41 (24) |
| Grade >= 3 | 14 (8) | 37 (22) |
| Chills | 47 (28) | 14 (8) |

| | | |
|---|---|---|
| Grade >= 3 | 1 (1) | 0 (0) |
| Cough | 42 (25) | 18 (11) |
| Grade >= 3 | 1 (1) | 0 (0) |
| Dizziness | 36 (21) | 21 (13) |
| Grade >= 3 | 2 (1) | 1 (1) |
| Hypomagnesaemia | 20 (12) | 34 (20) |
| Grade >= 3 | 1 (1) | 4 (2) |
| Lymphocyte count decreased | 31 (18) | 21 (13) |
| Grade >= 3 | 29 (17) | 18 (11) |
| Febrile neutropenia | 4 (2) | 46 (27) |
| Grade >= 3 | 4 (2) | 46 (27) |
| Hypoxia | 37 (22) | 13 (8) |
| Grade >= 3 | 16 (9) | 7 (4) |
| Abdominal pain | 24 (14) | 25 (15) |
| Grade >= 3 | 5 (3) | 2 (1) |
| Oedema peripheral | 20 (12) | 28 (17) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Alanine aminotransferase increased | 31 (18) | 16 (10) |
| Grade >= 3 | 1 (1) | 3 (2) |
| Insomnia | 21 (12) | 26 (15) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Tremor | 44 (26) | 1 (1) |
| Grade >= 3 | 2 (1) | 0 (0) |
| Confusional state | 40 (24) | 4 (2) |
| Grade >= 3 | 9 (5) | 0 (0) |
| Hyperglycaemia | 27 (16) | 17 (10) |
| Grade >= 3 | 7 (4) | 5 (3) |
| Hypocalcaemia | 27 (16) | 17 (10) |
| Grade >= 3 | 1 (1) | 3 (2) |
| Back pain | 16 (9) | 25 (15) |
| Grade >= 3 | 0 (0) | 4 (2) |
| Aspartate aminotransferase increased | 24 (14) | 15 (9) |
| Grade >= 3 | 1 (1) | 1 (1) |
| Aphasia | 36 (21) | 0 (0) |
| Grade >= 3 | 12 (7) | 0 (0) |
| Acute kidney injury | 13 (8) | 21 (13) |
| Grade >= 3 | 3 (2) | 4 (2) |
| Dyspnoea | 14 (8) | 20 (12) |

| | | |
|---|---|---|
| Grade >= 3 | 5 (3) | 2 (1) |
| Hypoalbuminaemia | 22 (13) | 12 (7) |
| Grade >= 3 | 1 (1) | 0 (0) |
| Stomatitis | 5 (3) | 29 (17) |
| Grade >= 3 | 0 (0) | 3 (2) |
| Arthralgia | 19 (11) | 14 (8) |
| Grade >= 3 | 1 (1) | 1 (1) |
| Encephalopathy | 29 (17) | 2 (1) |
| Grade >= 3 | 20 (12) | 0 (0) |
| Asthenia | 14 (8) | 16 (10) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Hyponatraemia | 21 (12) | 8 (5) |
| Grade >= 3 | 10 (6) | 4 (2) |
| Muscular weakness | 19 (11) | 10 (6) |
| Grade >= 3 | 6 (4) | 0 (0) |
| Hiccups | 5 (3) | 21 (13) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Malaise | 17 (10) | 9 (5) |
| Grade >= 3 | 0 (0) | 0 (0) |
| Somnolence | 19 (11) | 2 (1) |
| Grade >= 3 | 5 (3) | 0 (0) |
| Hypogammaglobulinaemia | 19 (11) | 1 (1) |
| Grade >= 3 | 0 (0) | 0 (0) |
| Mucosal inflammation | 1 (1) | 16 (10) |
| Grade >= 3 | 0 (0) | 6 (4) |

TEAEs by Severity:

The worst Grade 3 or higher TEAEs that were most frequently (≥ 10% of subjects) reported in each treatment arm were generally hematologic AEs, as follows:

- Axicabtagene ciloleucel arm: Neutropenia (73 subjects, 43%); anemia (51 subjects, 30%); neutrophil count decreased (49 subjects, 29%); white blood cell count decreased (43 subjects, 25%); hypophosphatemia (31 subjects, 18%); lymphocyte count decreased (29 subjects, 17%); encephalopathy (20 subjects, 12%); and hypotension (19 subjects, 11%)
- SOCT arm: Anemia (65 subjects, 39%); platelet count decreased (60 subjects, 36%); neutrophil count decreased (47 subjects, 28%); febrile neutropenia (46 subjects, 27%); thrombocytopenia (37 subjects, 22%); white blood cell count decreased (31 subjects, 18%); neutropenia (28 subjects, 17%); hypophosphatemia (21 subjects, 13%); lymphocyte count decreased (18 subjects, 11%)

The most frequently (≥ 10% of subjects in either treatment arm) reported non-hematologic worst Grade 3 or higher TEAEs were hypophosphatemia (31 subjects, 18%), encephalopathy (20 subjects, 12%), and hypotension (19 subjects, 11%) for the axicabtagene ciloleucel arm and hypophosphatemia (21 subjects, 13%) for the SOCT arm.

TEAEs related to treatment arms:

**Table 23. Incidence of Treatment-related TEAEs by PT and Worst Grade Occurring in ≥ 10% of Subjects in Either Treatment Arm (Safety Analysis Set); source m5.3.5.1 Report Body**

| Preferred Term<br>Worst CTCAE Grade | Axicabtagene Ciloleucel<br>(N = 170)<br>n (%) | Standard of Care<br>(N = 168)<br>n (%) |
|---|---|---|
| Subjects with any treatment-related TEAE | 163 (96) | 160 (95) |
| Grade 1 | 10 (6) | 15 (9) |
| Grade 2 | 41 (24) | 14 (8) |
| Grade 3 | 50 (29) | 35 (21) |
| Grade 4 | 61 (36) | 94 (56) |
| Grade 5 | 1 (1) | 2 (1) |
| Grade >= 3 | 112 (66) | 131 (78) |
| Pyrexia | 157 (92) | 33 (20) |
| Grade >= 3 | 15 (9) | 0 (0) |
| Nausea | 30 (18) | 108 (64) |
| Grade >= 3 | 2 (1) | 9 (5) |
| Fatigue | 50 (29) | 80 (48) |
| Grade >= 3 | 9 (5) | 4 (2) |
| Anaemia | 25 (15) | 83 (49) |
| Grade >= 3 | 16 (9) | 62 (37) |
| Hypotension | 70 (41) | 18 (11) |

| | | |
|---|---|---|
| Grade >= 3 | 18 (11) | 4 (2) |
| Headache | 51 (30) | 27 (16) |
| Grade >= 3 | 4 (2) | 0 (0) |
| Diarrhoea | 24 (14) | 52 (31) |
| Grade >= 3 | 2 (1) | 6 (4) |
| Neutropenia | 48 (28) | 28 (17) |
| Grade >= 3 | 43 (25) | 27 (16) |
| Neutrophil count decreased | 22 (13) | 45 (27) |
| Grade >= 3 | 21 (12) | 45 (27) |
| Vomiting | 17 (10) | 49 (29) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Platelet count decreased | 7 (4) | 58 (35) |
| Grade >= 3 | 4 (2) | 54 (32) |
| Decreased appetite | 24 (14) | 40 (24) |
| Grade >= 3 | 6 (4) | 6 (4) |
| Sinus tachycardia | 51 (30) | 9 (5) |
| Grade >= 3 | 3 (2) | 1 (1) |
| Thrombocytopenia | 16 (9) | 39 (23) |
| Grade >= 3 | 12 (7) | 35 (21) |
| Chills | 45 (26) | 8 (5) |
| Grade >= 3 | 1 (1) | 0 (0) |
| White blood cell count decreased | 13 (8) | 37 (22) |
| Grade >= 3 | 12 (7) | 31 (18) |
| Hypokalaemia | 7 (4) | 39 (23) |
| Grade >= 3 | 1 (1) | 9 (5) |
| Constipation | 2 (1) | 43 (26) |
| Grade >= 3 | 0 (0) | 0 (0) |
| Febrile neutropenia | 1 (1) | 43 (26) |
| Grade >= 3 | 1 (1) | 43 (26) |
| Hypoxia | 33 (19) | 7 (4) |
| Grade >= 3 | 14 (8) | 3 (2) |
| Tremor | 37 (22) | 1 (1) |
| Grade >= 3 | 2 (1) | 0 (0) |

| | | |
|---|---|---|
| Confusional state | 35 (21) | 1 (1) |
| Grade >= 3 | 8 (5) | 0 (0) |
| Aphasia | 35 (21) | 0 (0) |

| | | |
|---|---|---|
| Grade >= 3 | 12 (7) | 0 (0) |
| Hypophosphataemia | 9 (5) | 25 (15) |
| Grade >= 3 | 6 (4) | 18 (11) |
| Hypomagnesaemia | 5 (3) | 27 (16) |
| Grade >= 3 | 1 (1) | 2 (1) |
| Dizziness | 14 (8) | 16 (10) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Encephalopathy | 29 (17) | 1 (1) |
| Grade >= 3 | 20 (12) | 0 (0) |
| Alanine aminotransferase increased | 13 (8) | 16 (10) |
| Grade >= 3 | 1 (1) | 3 (2) |
| Stomatitis | 1 (1) | 28 (17) |
| Grade >= 3 | 0 (0) | 3 (2) |
| Lymphocyte count decreased | 5 (3) | 21 (13) |
| Grade >= 3 | 5 (3) | 18 (11) |
| Acute kidney injury | 7 (4) | 17 (10) |
| Grade >= 3 | 0 (0) | 4 (2) |
| Hiccups | 2 (1) | 17 (10) |
| Grade >= 3 | 0 (0) | 1 (1) |
| Hypogammaglobulinaemia | 17 (10) | 1 (1) |
| Grade >= 3 | 0 (0) | 0 (0) |
| Somnolence | 18 (11) | 0 (0) |
| Grade >= 3 | 4 (2) | 0 (0) |
| Mucosal inflammation | 0 (0) | 16 (10) |
| Grade >= 3 | 0 (0) | 6 (4) |

Treatment-related TEAEs of any grade that were most frequently (≥ 30% of subjects) reported in each treatment arm were as follows:

- Axicabtagene ciloleucel arm: Pyrexia (157 subjects, 92%), hypotension (70 subjects, 41%), and headache and sinus tachycardia (51 subjects each, 30%)
- SOCT arm: Nausea (108 subjects, 64%), anemia (83 subjects, 49%), fatigue (80 subjects, 48%), platelet count decreased (58 subjects, 35%), and diarrhea (52 subjects, 31%)

Treatment-related worst Grade 3 or higher TEAEs that were most frequently (≥ 10% of subjects) reported in each treatment arm were as follows:

- Axicabtagene ciloleucel arm: Neutropenia (43 subjects, 25%), neutrophil count decreased (21 subjects, 12%), encephalopathy (20 subjects, 12%), and hypotension (18 subjects, 11%)
- SOCT arm: Anemia (62 subjects, 37%), platelet count decreased (54 subjects, 32%), neutrophil count decreased (45 subjects, 27%), febrile neutropenia (43 subjects, 26%), thrombocytopenia (35 subjects, 21%), white blood cell count decreased (31 subjects, 18%), neutropenia (27

subjects, 16%), hypophosphatemia (18 subjects, 11%), and lymphocyte count decreased (18 subjects, 11%)

Adverse events related to procedures before axicabtagene ciloleucel infusion:

- At least 1 AE related to **leukapheresis** was reported for 27 of 170 subjects (16%) who later received axicabtagene ciloleucel, including 5 subjects (3%) with worst Grade 3 or higher leukapheresis-related AEs (Report Body Table 14.3.1.2.9). One subject (1%) had a worst Grade 4 AE, and no subjects had a Grade 5 AE related to leukapheresis.
- At least 1 AE related to **lymphodepleting chemotherapy** was reported for 151 of 170 subjects (89%) who later received axicabtagene ciloleucel, including 130 subjects (76%) with worst Grade 3 or higher lymphodepleting chemotherapy-related AEs (Report Body Table 14.3.1.2.10). Worst Grade 4 lymphodepleting chemotherapy-related AEs were reported for 109 subjects (64%), and 1 subject (1%) had a Grade 5 AE of PML (source Report Body Section 15.3 subject narrative). The 3 most common AEs of any grade reported as related to lymphodepleting chemotherapy were nausea and neutropenia (63 subjects each, 37%), and anemia (59 subjects, 35%). The 3 most common worst Grade 3 or higher lymphodepleting chemotherapy-related AEs were neutropenia (61 subjects, TEAEs of Special Interest:

Neurologic Events

**Table 24. Treatment-emergent Neurologic Events Occurring in ≥ 5% of Subjects in Either Treatment Arm by PT and Worst Grade (Safety Analysis Set)**

| Preferred Term<br>Worst CTCAE Grade | Axicabtagene Ciloleucel<br>(N = 170)<br>n (%) | Standard of Care<br>(N = 168)<br>n (%) |
|---|---|---|
| Subjects with any TE neurologic events | 102 (60) | 33 (20) |
| Grade 1 | 42 (25) | 23 (14) |
| Grade 2 | 24 (14) | 9 (5) |
| Grade 3 | 26 (15) | 1 (1) |
| Grade 4 | 10 (6) | 0 (0) |
| Grade 5 | 0 (0) | 0 (0) |
| Grade >= 3 | 36 (21) | 1 (1) |
| Tremor | 44 (26) | 1 (1) |
| Grade >= 3 | 2 (1) | 0 (0) |
| Confusional state | 40 (24) | 4 (2) |
| Grade >= 3 | 9 (5) | 0 (0) |
| Aphasia | 36 (21) | 0 (0) |
| Grade >= 3 | 12 (7) | 0 (0) |
| Encephalopathy | 29 (17) | 2 (1) |
| Grade >= 3 | 20 (12) | 0 (0) |
| Paraesthesia | 8 (5) | 14 (8) |
| Grade >= 3 | 1 (1) | 0 (0) |
| Somnolence | 19 (11) | 2 (1) |
| Grade >= 3 | 5 (3) | 0 (0) |

| | | |
|---|---|---|
| Agitation | 10 (6) | 2 (1) |
| Grade >= 3 | 4 (2) | 0 (0) |
| Mental status changes | 10 (6) | 0 (0) |
| Grade >= 3 | 4 (2) | 0 (0) |
| Hypoaesthesia | 8 (5) | 1 (1) |
| Grade >= 3 | 2 (1) | 0 (0) |

Serious treatment-emergent neurologic events of any grade were reported for 34 subjects (20%) in the axicabtagene ciloleucel arm and 1 subject (1%) in the SOCT arm, including 26 subjects (15%) in the axicabtagene ciloleucel arm with a serious worst Grade 3 or higher neurologic event and 1 subject (1%) in the SOCT arm with a serious worst Grade 2 neurologic event. The 3 most common serious treatment-emergent neurologic events of any grade in the axicabtagene ciloleucel arm were encephalopathy (17 subjects, 10%), aphasia (9 subjects, 5%), and confusional state (6 subjects, 4%), and the only serious neurologic event in the SOCT arm was encephalopathy.

Treatment-related neurologic events were reported for 92 subjects (54%) in the axicabtagene ciloleucel arm and 24 subjects (14%) in the SOCT arm, including 35 subjects (21%) and 1 subject (1%), respectively, with Grade 3 or higher neurologic events. The most frequently reported (in ≥ 10% of subjects) treatment-related neurologic events of any grade in the axicabtagene ciloleucel arm were tremor (37 subjects, 22%), confusional state (35 subjects, 21%), aphasia (35 subjects, 21%), encephalopathy (29 subject, 17%), and somnolence (18 subjects, 11%).

No treatment-related neurologic events occurred with a subject incidence higher than 10% in the SOCT arm: the most frequently reported treatment-related neurologic events in the SOCT arm were paresthesia (9 subjects, 5%), agitation, lethargy, cognitive disorder, depressed level of consciousness, delirium, and taste disorder (2 subjects each, 1%).

Serious treatment-related neurologic events were reported for 32 subjects (19%) in the axicabtagene ciloleucel arm, including 25 subjects (15%) with Grade 3 or higher serious neurologic events. No subject in the SOCT arm had a serious treatment related neurologic event. The most frequently reported (in ≥ 2% of subjects) serious treatment-related neurologic events of any grade in the axicabtagene ciloleucel arm were encephalopathy (17 subjects, 10%), aphasia (9 subjects, 5%), and confusional state, somnolence, and tremor (5 subjects each, 3%).

Among subjects who had a treatment-emergent neurologic event, the median time to onset was 7.0 days (range: 1 to 133 days) after the axicabtagene ciloleucel infusion and 23.0 days (range: 1 to 108 days) after the first dose of standard of care salvage chemotherapy.

At the data cutoff date, neurologic events had resolved in 96 of the 102 subjects in the axicabtagene ciloleucel arm and in 32 of the 33 subjects in the SOCT arm. A total of 6 subjects in the axicabtagene ciloleucel arm and 1 subject in the SOCT arm had ongoing neurologic events at the data cutoff date or unresolved neurologic events at the time of death (source Listing 16.3.4.1.2 and Listing 16.3.7). Among subjects in the axicabtagene ciloleucel arm, 1 subject had ongoing neurologic events as of the data cutoff date and 5 subjects had neurologic events that were unresolved at the time of death, as follows:

- One subject had Grade 2 non-serious paresthesia of the lower limbs that started on Therapy day 16 and Grade 1 non-serious memory impairment that started on Therapy day 17; both events were ongoing at the data cutoff date. The event of paresthesia was deemed unrelated to leukapheresis or study treatments and memory impairment was deemed related to axicabtagene ciloleucel.

- One subject had Grade 1 non-serious tremor, which started on Therapy day 5 and was unresolved at the time of death due to PD on Therapy day 200. The event was deemed related to axicabtagene ciloleucel.
- One subject had Grade 1 non-serious taste disorder, which started on Therapy day 37 and was unresolved at the time of death due to PD on Therapy day 240. The event was deemed related to lymphodepleting chemotherapy.
- One subject had Grade 2 non-serious confusion and Grade 2 non-serious hallucination that both started on Therapy day 37, Grade 1 non-serious paresthesia that started on Therapy day 38, Grade 2 non-serious agitation that started on Therapy day 43, and Grade 4 non-serious depressed level of consciousness and Grade 3 non-serious somnolence that both started on Therapy day 45. These events were unresolved at the time of death due to PD on Therapy day 46. The events were deemed unrelated to leukapheresis or study treatments.
- One subject had Grade 1 non-serious hypoesthesia, which started on Therapy day 77 and was unresolved at the time of death due to PD on Therapy day 326. The event was deemed unrelated to leukapheresis or study treatments.
- One subject had Grade 2 non-serious tremor, which started on Therapy day 4, changed to a Grade 3 serious event on Therapy day 13, and changed to a Grade 2 non-serious event on Therapy day 24 (Listing 16.3.2.1) and was unresolved at the time of death due to PD on Therapy day 206. The event was deemed related to axicabtagene ciloleucel.

One subject in the SOCT arm had an ongoing neurologic event of Grade 1 non-serious paresthesia, which started on Therapy day 20 and was ongoing at the data cutoff date. The event was deemed related to SOCT (source Listing 16.3.4.1.2).

Important Identified Risks (axicabtagene ciloleucel arm and SOCT arm)

CRS

CRS, an identified risk for axicabtagene ciloleucel, but not for agents used as SOCT, was reported for n=157/170 subjects (92%) in the axicabtagene ciloleucel arm; 8 subjects (5%) had worst Grade 3 CRS, 3 subjects (2%) had worst Grade 4 CRS, and no subjects had Grade 5 CRS. The most frequently reported CRS symptoms (in ≥ 30% of subjects with CRS) were pyrexia (155 subjects, 99%), hypotension (68 subjects, 43%), and sinus tachycardia (49 subjects, 31%). The median time of onset was 3 days (range: 1 to 10 days), and at DCO CRS was resolved in all subjects, with a median duration of 7 days (range: 2 to 43 days).

Cytopenias

49 subjects (29%) in the axicabtagene ciloleucel arm and 101 subjects (60%) in the SOCT arm had a prolonged worst Grade 3 or higher cytopenia event. The number of subjects in the axicabtagene ciloleucel arm who had worst Grade 3 or higher prolonged thrombocytopenia, neutropenia, or anemia TEAEs were 11 (6%), 44 (26%), and 5 (3%), respectively. The number of subjects treated with SOCT who had worst Grade 3 or higher prolonged thrombocytopenia, neutropenia, and anemia TEAEs were 78 (46%), 60 (36%), and 57 (34%), respectively.

**Table 25. Cytopenia TEAEs by PT (Safety Analysis Set); source Report Body**

| Adverse Events Group, n (%)<br>Preferred Term, n (%) | **Axicabtagene Ciloleucel (N=170)** | | **Standard of Care (N=168)** | |
|---|---|---|---|---|
| | Any Grade<br>n (%) | Grade ≥ 3<br>n (%) | Any Grade<br>n (%) | Grade ≥3<br>n (%) |

| | | | | |
|---|---|---|---|---|
| Subjects with any event | 136 (80) | 128 (75) | 135 (80) | 126 (75) |
| Subjects with thrombocytopenia | 50 (29) | 25 (15) | 101 (60) | 95 (57) |
| Platelet count decreased | 30 (18) | 12 (7) | 64 (38) | 60 (36) |
| Thrombocytopenia | 22 (13) | 14 (8) | 41 (24) | 37 (22) |
| Subjects with neutropenia | 122 (72) | 119 (70) | 92 (55) | 91 (54) |
| Neutropenia | 75 (44) | 73 (43) | 29 (17) | 28 (17) |
| Neutrophil count decreased | 52 (31) | 49 (29) | 47 (28) | 47 (28) |
| Febrile neutropenia | 4 (2) | 4 (2) | 46 (27) | 46 (27) |
| Subjects with anaemia | 73 (43) | 51 (30) | 92 (55) | 65 (39) |
| Anaemia | 71 (42) | 51 (30) | 91 (54) | 65 (39) |
| Haemoglobin decreased | 1 (1) | 0 (0) | 1 (1) | 0 (0) |
| Anaemia macrocytic | 1 (1) | 0 (0) | 0 (0) | 0 (0) |
| Haematocrit decreased | 1 (1) | 0 (0) | 0 (0) | 0 (0) |

**Table 26. Prolonged Cytopenias Present on or After Therapy Day 30 (Safety Analysis Set); source Report Body**

| | **Axicabtagene Ciloleucel (N=170)** | | **Standard of Care (N=168)** | |
|---|---|---|---|---|
| Adverse Events Group, n (%)<br>Preferred Term, n (%) | Any Grade<br>n (%) | Grade ≥3<br>n (%) | Any Grade<br>n (%) | Grade ≥3<br>n (%) |
| Subjects with any prolonged event | 70 (41) | 49 (29) | 117 (70) | 101 (60) |
| Subjects with prolonged thrombocytopenia | 32 (19) | 11 (6) | 85 (51) | 78 (46) |
| Platelet count decreased | 17 (10) | 5 (3) | 53 (32) | 47 (28) |
| Thrombocytopenia | 16 (9) | 6 (4) | 35 (21) | 33 (20) |
| Subjects with prolonged neutropenia | 56 (33) | 44 (26) | 61 (36) | 60 (36) |
| Neutrophil count decreased | 26 (15) | 20 (12) | 28 (17) | 28 (17) |
| Neutropenia | 29 (17) | 22 (13) | 21 (13) | 20 (12) |
| Febrile neutropenia | 4 (2) | 4 (2) | 36 (21) | 36 (21) |
| Subjects with prolonged anaemia | 23 (14) | 5 (3) | 84 (50) | 57 (34) |
| Anaemia | 22 (13) | 5 (3) | 83 (49) | 57 (34) |
| Anaemia macrocytic | 1 (1) | 0 (0) | 0 (0) | 0 (0) |
| Haematocrit decreased | 1 (1) | 0 (0) | 0 (0) | 0 (0) |
| Haemoglobin decreased | 0 (0) | 0 (0) | 1 (1) | 0 (0) |

Infections

In the safety analysis set, 70 subjects (41%) in the axicabtagene ciloleucel arm and 51 subjects (30%) in the SOCT arm had at least 1 treatment-emergent infection, including 24 subjects (14%) and 19 subjects (11%), respectively, with worst Grade 3 or higher infections. Three subjects (2%) in the axicabtagene ciloleucel arm and 6 subjects (4%) in the SOCT arm had worst Grade 4 infections. Five subjects (3%) in the axicabtagene ciloleucel arm had a Grade 5 TEAE of infection (2 subjects with COVID-

19, 1 subject with PML, 1 subject with hepatitis B reactivation, and 1 subject with sepsis; whereas no subjects in the SOCT arm had a Grade 5 TEAE of infection.

The most frequently (in ≥ 5% of subjects) reported infection categories were unspecified infections (44 subjects, 26%), viral infections (26 subjects, 15%), bacterial infections (16 subjects, 9%), upper respiratory tract infections (11 subjects, 6%), and opportunistic infections (8 subjects, 5%) in the axicabtagene ciloleucel arm and unspecified (40 subjects, 24%), bacterial infections (15 subjects, 9%), and viral infections (8 subjects, 5%) in the SOCT arm. Five subjects (3%) in the axicabtagene ciloleucel arm had a Grade 5 TEAE of infection (2 subjects with COVID-19, 1 subject with PML, 1 subject with hepatitis B reactivation, and 1 subject with sepsis); whereas no subjects in the SOCT arm had a Grade 5 TEAE of infection. A Grade 1 COVID-19 infection was reported for one subject (1%) in the SOCT arm.

Hypogammaglobulinemia

Among subjects in the axicabtagene ciloleucel, 19 subjects (11%) had a hypogammaglobulinemia event, of whom all subjects had TEAEs with a PT of hypogammaglobulinemia that were worst Grade 1 (6 subjects, 4%) or Grade 2 (13 subjects, 8%).

Among subjects treated with the SOCT, 1 subject (1%) had at least one worst Grade 1 hypogammaglobulinemia event (PT = hypogammaglobulinemia).

Important Potential Risks (axicabtagene ciloleucel arm)

No subject in either treatment arm had treatment-emergent aggravation of GVHD or treatment-related tumor lysis syndrome. No subject in the axicabtagene ciloleucel arm tested positive for RCR or was confirmed to be antibody-positive after axicabtagene ciloleucel infusion, or had a new malignancy considered by Kite to be secondary to axicabtagene. Cardiac symptoms, such as sinus tachycardia were identified.

## *Serious adverse event/deaths/other significant events*

SAEs

SAES were reported for 85 subjects (50%) treated with axicabtagene ciloleucel and 77 subjects (46%) treated with SOCT. The most frequently reported (≥ 5% of subjects) SAEs in the axicabtagene ciloleucel arm were pyrexia (27 subjects, 16%), encephalopathy (17 subjects, 10%), hypotension (15 subjects, 9%), aphasia (9 subjects, 5%) and pneumonia (8 subjects, 5%); and in the SOCT arm were febrile neutropenia (22 subjects, 13%), and acute kidney injury and pyrexia (8 subjects each, 5%).

The most frequently reported (> 2% of subjects) worst Grade 3 or higher SAEs, excluding B -cell lymphoma, in the axicabtagene ciloleucel arm were encephalopathy (15 subjects, 9%), aphasia (8 subjects, 5%), hypotension (7 subjects, 4%), and pneumonia (6 subjects, 4%); and in the SOCT arm were febrile neutropenia (22 subjects, 13%) and platelet count decreased (5 subjects, 3%).

The most frequently reported (≥ 5% of subjects) axicabtagene ciloleucel-related SAEs were pyrexia (24 subjects, 14%), encephalopathy (17 subjects, 10%), hypotension (15 subjects, 9%), and aphasia (9 subjects, 5%); and the most frequently reported SOCT-related SAE was febrile neutropenia (19 subjects, 11%).

Deaths

At the data cutoff date, 142 of 338 subjects (42%) in the safety analysis set had died, including 64 subjects (38%) in the axicabtagene ciloleucel arm and 78 subjects (46%) in the SOCT arm.

- One hundred and eleven subjects (33%) died due to PD (47 subjects [28%] in the axicabtagene ciloleucel arm and 64 subjects [38%] in the SOCT arm)
- Eight subjects (2%) died due to TEAEs (6 subjects [4%] in the axicabtagene ciloleucel arm and 2 subjects [1%] in the SOCT arm):

  One subject in the axicabtagene ciloleucel arm died on Therapy day 53 due to myocardial infarction that was deemed unrelated to study treatment

  One subject in the axicabtagene ciloleucel arm died on Therapy day 207 due to progressive multifocal leukoencephalopathy (PML) that was deemed related to lymphodepleting chemotherapy

  One subject in the axicabtagene ciloleucel arm died on Therapy day 422 due to hepatitis B reactivation that was deemed related to axicabtagene ciloleucel

  One subject in the axicabtagene ciloleucel arm died on Therapy day 442 due to sepsis that was deemed unrelated to study treatment

  Two subjects in the axicabtagene ciloleucel arm died, 1 subject on Therapy day 275 and 1 subject on Therapy day 278, due to COVID-19; both were deemed unrelated to study treatment

  One subject in the SOCT arm died on Therapy day 146 due to cardiac arrest that was deemed related to HDT (a component of SOCT)

  One subject in the SOCT arm died on Therapy day 161 due to acute respiratory distress syndrome that was deemed related to HDT (a component of SOCT)
- The death of 1 subject (1%) in the axicabtagene ciloleucel arm was reported by the investigator as "secondary malignancy" (lung adenocarcinoma), although deemed by the investigator to be unrelated to axicabtagene ciloleucel. (event was reported as a Grade 5 TEAE)
- Twenty-two subjects (7%) died due to reasons reported as "other" (10 subjects [6%] in the axicabtagene ciloleucel arm and 12 subjects [7%] in the SOCT arm), which included 2 subjects (1%) in each treatment arm with COVID-19 that occurred outside the AE reporting window.

### *Laboratory findings*

Subject incidences of changes in clinical chemistry values reported in ≥ 10% of subjects in either the pooled axicabtagene ciloleucel population or the SOCT arm of ZUMA-7 are as follows:

- Increases in glucose (90% and 64%, respectively), and decreases in glucose (13% and 8%, respectively),
- Increases in creatinine (83% and 77%, respectively),
- Increases in alanine aminotransferase (77% and 43%, respectively),
- Increases in aspartate aminotransferase (65% and 33%, respectively), increases in alkaline phosphatase (37% and 43%, respectively), increases in bilirubin (34% and 11%, respectively),
- Decreases in calcium (96% and 48%, respectively),
- Decreases in albumin (90% and 37%, respectively),
- Decreases in magnesium (88% and 74%, respectively), decreases in sodium (82% and 31%, respectively), decreases in potassium (56% and 25%, respectively), decreases in phosphate (40% and 6%, respectively).

Of the most frequently reported changes in clinical chemistry parameters of any grade, the following were reported numerically more frequently (by ≥ 10%) in the pooled axicabtagene ciloleucel population than in the SOCT arm of ZUMA-7: increases in glucose, alanine aminotransferase, aspartate aminotransferase, and bilirubin, and decreases in calcium, albumin, magnesium, sodium, potassium, and phosphate.

The subject incidences of changes in clinical chemistry values of worst Grade 3 or higher that were reported in ≥ 10% of subjects in either treatment arm were as follows: increases in glucose (10% and 5%, respectively), decreases in sodium (16% and 2%, respectively), and decreases in phosphate (23% and 5%).

*ZUMA-1 (supportive data) and Pooled Analyses of TEAEs*

**Table 27. Overall Summary of TEAEs: ZUMA-7, ZUMA-1, and the Pooled Axicabtagene Ciloleucel Population of ZUMA-7 and ZUMA-1 (Safety Analysis Set)**

| | SOCT | Axicabtagene Ciloleucel | | |
|---|---|---|---|---|
| | ZUMA-7 (N = 168) | ZUMA-7 (N = 170) | ZUMA-1 (N = 108) | Overall (N = 278) |
| Subject Incidence | n (%) | n (%) | n (%) | n (%) |
| Any TEAE | 168 (100) | 170 (100) | 108 (100) | 278 (100) |
| Worst Grade ≥ 3 | 140 (83) | 155 (91) | 104 (96) | 259 (93) |
| Worst Grade 5 | 7 (4) | 14 (8) | 9 (8) | 23 (8) |
| Due to disease progression | 5 (3) | 7 (4) | 5 (5) | 12 (4) |
| Any serious TEAE | 77 (46) | 85 (50) | 58 (54) | 143 (51) |
| Worst Grade ≥ 3 | 67 (40) | 72 (42) | 53 (49) | 125 (45) |
| Worst Grade 5 | 6 (4) | 14 (8) | 9 (8) | 23 (8) |
| Due to disease progression | 4 (2) | 7 (4) | 5 (5) | 12 (4) |
| Any axicabtagene ciloleucel/ SOCT-related TEAE | 160 (95) | 163 (96) | 107 (99) | 270 (97) |
| Worst Grade ≥ 3 | 131 (78) | 112 (66) | 72 (67) | 184 (66) |
| Worst Grade 5 | 2 (1) | 1 (1) | 2 (2) | 3 (1) |
| Any serious axicabtagene ciloleucel/SOCT related TEAE | 59 (35) | 63 (37) | 40 (37) | 103 (37) |
| Worst Grade ≥ 3 | 51 (30) | 49 (29) | 36 (33) | 85 (31) |
| Worst Grade 5 | 2 (1) | 1 (1) | 2 (2) | 3 (1) |
| Any CRS or neurologic event | NA | 159 (94) | 101 (94) | 260 (94) |
| Worst Grade ≥ 3 | NA | 41 (24) | 39 (36) | 80 (29) |
| Worst Grade 5 | NA | 0 (0) | 1 (1) | 1 (0) |
| Any CRS | NA | 157 (92) | 100 (93) | 257 (92) |
| Worst Grade ≥ 3 | NA | 11 (6) | 12 (11) | 23 (8) |
| Worst Grade 5 | NA | 0 (0) | 1 (1) | 1 (0) |
| Any serious CRS | NA | 29 (17) | -- | NA |
| Worst Grade ≥ 3 | NA | 10 (6) | -- | NA |
| Worst Grade 5 | NA | 0 (0) | -- | NA |
| Any neurologic event | 33 (20) | 102 (60) | 71 (66) | 173 (62) |
| Worst Grade ≥ 3 | 1 (1) | 36 (21) | 34 (31) | 70 (25) |
| Worst Grade 5 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Any serious neurologic event | 1 (1) | 34 (20) | 27 (25) | 61 (22) |

| Subject Incidence | SOCT | Axicabtagene Ciloleucel | | |
|---|---|---|---|---|
| | ZUMA-7 (N = 168) n (%) | ZUMA-7 (N = 170) n (%) | ZUMA-1 (N = 108) n (%) | Overall (N = 278) n (%) |
| Worst Grade ≥ 3 | 0 (0) | 26 (15) | 25 (23) | 51 (18) |
| Worst Grade 5 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Any infection | 51 (30) | 70 (41) | 43 (40) | 113 (41) |
| Worst Grade ≥ 3 | 19 (11) | 24 (14) | 29 (27) | 53 (19) |
| Worst Grade 5 | 0 (0) | 5 (3) | 0 (0) | 5 (2) |
| Any cytopenias | 135 (80) | 136 (80) | 98 (91) | 234 (84) |
| Worst Grade ≥ 3 | 126 (75) | 128 (75) | 89 (82) | 217 (78) |
| Worst Grade 5 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Any hypogammaglobulinemia | 1 (1) | 19 (11) | 17 (16) | 36 (13) |
| Worst Grade ≥ 3 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Worst Grade 5 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

### *Discontinuation due to adverse events*

No subject discontinued treatment due to TEAE in the axicabtagene ciloleucel arm. Two subjects in the SOCT arm discontinued treatment due to TEAEs of Grade 4 acute kidney injury and Grade 1 blood stem cell harvest failure.

### *Post marketing experience*

Axicabtagene ciloleucel is approved under the trade name YESCARTA in 38 countries including the US, the European Economic Area (comprising 30 countries), United Kingdom, Switzerland, Canada, Australia, Israel, Japan, and China.

A post-marketing risk mitigation program includes administration of axicabtagene ciloleucel at qualified sites that have demonstrated availability of tocilizumab for use in managing CRS and neurologic events and educational materials for healthcare providers and patients. A long-term post-marketing study will follow patients who have received YESCARTA for 15 years and will assess the long-term safety, assess the risk of new malignancy, further characterize important risks, and identify new signals.

Post-marketing data are provided from the most recently available periodic safety update report/periodic benefit-risk evaluation report for axicabtagene ciloleucel (source m5.3.6). As of 17 April 2021, 808 subjects have been exposed to axicabtagene ciloleucel in company-sponsored interventional clinical studies. It is estimated that 4,497 patients have been exposed to axicabtagene ciloleucel in post-authorization use. No new identified or potential risks for axicabtagene ciloleucel have emerged following the commercialization of this product and the overall benefit-risk evaluation for axicabtagene ciloleucel continues to be positive.

## 2.6.1. Discussion on clinical safety

The Applicant provided a comprehensive safety data package for DCO 18 March 2021. The number of patients treated in ZUMA-7 was n=170 in the axicabtagene ciloleucel arm and n=168 in the SOCT arm. The median actual follow-up times of subjects in the axicabtagene ciloleucel and SOCT arms were 19.6

months and 18.0 months, respectively. At the date of data cutoff (18 March 2021), the ZUMA-7 study has ended for 37% of subjects who had received axicabtagene ciloleucel, and 48% who had received ≥ 1 dose of standard of care salvage chemotherapy. The primary reason for ending the study for subjects who received axicabtagene ciloleucel was death for 64 subjects (36%) and lost to follow-up for 2 subjects (1%). The primary reason for ending the study for subjects who received SOCT was death for 75 subjects (42%), withdrawal of consent for 7 subjects (4%), lost to follow-up for 2 subjects (1%), investigator decision for 1 subject (1%), and other reasons for 1 subject (1%).

Generally, there are no differences observed in number and grading of TEAEs in ZUMA-7 related to the procedures in the axicabtagene ciloleucel arm (leukapheresis, lymphodepletion and treatment), when comparing with the other clinical trials in the axicabtagene ciloleucel treatment program. TEAEs in both treatment arms have been treated according to general toxicity management recommendations, were generally manageable and resolved as of DCO; no new safety signals have been reported in either treatment arm. Regards TEAEs observed in the SOC arm, which mainly are pancytopenia, hypophosphatemia and febrile neutropenia, these can be considered specific side effect of agents in the permitted regimens for salvage SOCT, and there is no indication that number and/or grading of occurred TEAEs differ from them in the ZUMA-7 SOCT arm. All subjects treated (100%) in both arms had ≥ 1 TEAE. The number of grade 3 or higher TEAEs assessed related to the axicabtagene ciloleucel was n= 112 subjects (66%) versus n=131 (78%) in the SOCT arm. In the axicabtagene ciloleucel arm, 85 subjects (50%) had an SAE, and 72 subjects (42%) had a 3 or higher SAE. In the SOCT arm, 77 subjects (46%) had an SAE, and 67 subjects (40%) had a Grade 3 or higher SAE. The number of SAEs assessed related to axicabtagene ciloleucel and SOCT, respectively, was n= 63 subjects (37%) versus n=59 subjects (35%). Fatal TEAEs were reported for 7 subjects in the axicabtagene ciloleucel arm and 2 subjects in the SOCT arm. At the data cutoff date, 142 of 338 subjects (42%) in the safety analysis set had died, including 64 subjects (36%) in the axicabtagene ciloleucel arm and 75 subjects (42%) in the SOCT arm.

### 2.6.2. Conclusions on clinical safety

According to the provided data, no new major safety concerns arise from the new population as no additional safety issues in treatment with axicabtagene ciloleucel other than the known have been identified. Overall, the TEAEs and risks are similar to what has been described for other CAR T cell therapies and for axicabtagene ciloleucel in the other indications, and are manageable with the current risk minimization measures presented in the SmPC.

### 2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.7. Risk management plan*

The MAH submitted an updated RMP version 5.3. with this application.

This risk management plan (RMP) is submitted with an extension of indication based on the results from Study KTE-C19-107 (ZUMA-7), a phase 3, randomised, open-label study evaluating the efficacy of axicabtagene ciloleucel versus standard of care therapy in subjects with relapsed/refractory diffuse large B cell lymphoma (DLBCL).

The MAH submitted RMP version 7.1 with the responses to questions, sign off data 8 June 2022, addressing the assessment requests.

The MAH took the opportunity to upversion the RMP to version 8.0 to align the annexes version with another similar product from the same MAH; no changes in the body of the RMP were introduced.

The CAT received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.0 is acceptable.

The CAT endorsed this advice without changes.

The CAT endorsed the Risk Management Plan version 8.0 with the following content:

## *General comments*

The background for the RMP update was an update of the indication to include treatment of adult patients with relapsed or refractory high-grade b-cell lymphoma (HGBL). The restriction "after two or more lines of systemic therapy" in the indication DLBCL was removed; however, this still applies to PMBCL.

## *Safety concerns*

## *Module SI. Epidemiology of the indications and target population*

Module SI 'Epidemiology of the indication and target population' was updated satisfactorily to include epidemiology data for the proposed new indication of adult patients with relapsed or refractory high-grade B-cell lymphoma.

## *Module SIII. Clinical trial exposure*

Module SIII 'Clinical trial exposure' was updated with regard to information from ZUMA-7 about demographics, e.g. follow-up time, age group, gender and ethnic origin from ongoing clinical trials. In addition, cumulative subject exposure by study, age and race has been presented in tabular format, which is endorsed.

## *Module SIV. Populations not studied in clinical trials*

Module SIV 'Populations not studied in clinical trials' – SIV.1 was updated with the ZUMA-7 study exclusion criteria. Additionally, section SIV.2 and SIV.3 were updated to include data from the ZUMA-7 study. The proposed changes are acceptable.

## *Module SV Post-authorisation experience*

Module SV 'Post-authorisation experience' was updated with a new estimate of the post-marketing exposure stratified by geographic area. This is endorsed.

## *Module SVII. Identified and potential risks*

In the Module SVII, section SVII.3.1 'Presentation of important identified risks and important potential risks' has been adequately updated with data from the ZUMA-7 study.

In addition, the presentation of important identified and potential risks has been substantially revised and mainly shortened. The revisions are considered of editorial nature and represent an overall improvement of the messages in line with the RMP guidance. The changes are therefore acceptable.

In the characterisation of the risks, data from PASS KT-EU-471-0117 has been included, which is endorsed.

In section SVII.3.2 'Presentation of missing information', has been updated with data from the PASS KT-EU-471-0117, the cumulative post-marketing surveillance and ZUMA-7, as applicable. This is endorsed.

## *Module SVIII. Summary of the safety concerns*

No changes were proposed by the MAH to the summary of safety concerns. This is considered acceptable as initially no new safety concerns were identified from the submitted data.

**Table SVIII.1: Summary of the Safety Concerns**

| Summary of safety concerns | |
|---|---|
| Important identified risks | Serious neurologic adverse reactions including cerebral oedema<br>CRS<br>Cytopenias including aplastic anaemia<br>Infections<br>Hypogammaglobulinaemia |
| Important potential risks | Secondary malignancy<br>Immunogenicity<br>RCR<br>TLS<br>Aggravation of GvHD<br>Transmission of infectious agents via product<br>Decrease in viability of the product due to inappropriate preparation of infusion<br>CD19 negative relapse<br>CAR T persistence in relapsed patients<br>Failure to produce a viable CAR T cell product |
| Missing information | Use in pregnancy and lactation<br>Use in non-Caucasian patient populations<br>New occurrence or exacerbation of an autoimmune disorder<br>Long term safety |

## *Pharmacovigilance plan*

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| KT-EU-471-0117 (PASS): Long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory DLBCL and PMBCL<br>Ongoing | Additional characterization of the identified risks, further evaluation of potential risks and missing information. | Serious neurologic adverse reactions including cerebral oedema<br>CRS<br>Cytopenias including aplastic anaemia<br>Infections<br>Hypogammaglobulinemia<br>Secondary malignancy<br>RCR<br>TLS<br>Aggravation of GvHD<br>CD19 negative relapse<br>CAR T persistence in relapsed patients<br>Failure to produce a viable CAR T cell product<br>Use in pregnancy and lactation<br>New occurrence or exacerbation of an autoimmune disorder<br>Long term safety | Final Report Submission | 14 Nov 2040 |
| **Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| None | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| KTE-C19-101 (ZUMA-1)<br>A Phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL<br>Ongoing | To assess safety and efficacy of axicabtagene ciloleucel in refractory aggressive NHL | Serious neurologic adverse reactions including cerebral edema<br>CRS<br>Cytopenias including aplastic anemia<br>Infections<br>Hypogammaglobulinemia<br>Secondary malignancy<br>Immunogenicity<br>RCR<br>TLS<br>Aggravation of GvHD<br>CD19 negative relapse<br>CAR T persistence in relapsed patients<br>Failure to produce a viable CAR T cell product<br>Use in non-Caucasian patient populations<br>New occurrence of an autoimmune disorder<br>Long term safety | Safety updates in the nearest PSUR to the annual anniversary | Annual |
| | | | Final report Cohort 1 and 2 | 31 Aug 2031 |
| | | | Final report Cohort 3 | 31 Oct 2032 |
| KTE-C19-105 (ZUMA-5): A Phase 2 multicenter study of axicabtagene ciloleucel in subjects | To assess efficacy and safety of axicabtagene ciloleucel in subjects with | | Safety updates in the nearest PSUR to the annual | Annual |

| | | | | |
|---|---|---|---|---|
| with relapsed/refractory iNHL<br>Ongoing | relapsed/refractory iNHL | Serious neurologic adverse reactions including cerebral edema<br>CRS<br>Cytopenias including aplastic anemia<br>Infections<br>Hypogammaglobulinemia<br>Secondary malignancy<br>Immunogenicity<br>RCR<br>TLS<br>Aggravation of GvHD<br>CD19 negative relapse<br>CAR T persistence in relapsed patients<br>Failure to produce a viable CAR T cell product<br>Use in non-Caucasian patient populations<br>New occurrence of an autoimmune disorder<br>Long term safety | anniversary | |
| | | | Final report | 30 Apr 2036 |
| KTE-C19-106 (ZUMA-6): A Phase 1-2 multi-center study evaluating the safety and efficacy of KTE C19 in combination with Atezolizumab in subjects with refractory DLBCL<br>Ongoing | To assess efficacy and safety of axicabtagene ciloleucel in combination with atezolizumab in refractory DLBCL subjects | Serious neurologic adverse reactions including cerebral edema<br>CRS<br>Cytopenias including aplastic anemia<br>Infections<br>Hypogammaglobulinemia<br>Secondary malignancy<br>Immunogenicity<br>RCR<br>TLS<br>Aggravation of GvHD<br>CD19 negative relapse<br>CAR T persistence in relapsed patients<br>Failure to produce a viable CAR T cell product<br>Use in non-Caucasian patient populations<br>New occurrence of an autoimmune disorder<br>Long term safety | Safety updates in the nearest PSUR to the annual anniversary | Annual |
| | | | Final report | 31 Aug 2033 |

Only editorial changes were made to the overview of on-going and planned additional pharmacovigilance activities, which are acceptable.

Pending the outcome of this procedure and with the next regulatory opportunity, the MAH is reminded to reflect the extension of indication in future amendments of the study protocol of the imposed category one KT-EU-471-0117 PASS.

## *Overall conclusions on the PhV Plan*

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The study(ies) in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

## *Plans for post-authorisation efficacy studies*

There are no planned or ongoing post-authorization efficacy studies.

## *Risk minimisation measures*

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important identified risk(s)** | | |
| Serious neurologic adverse reactions including cerebral edema | **Routine risk minimization measures**:<br>SmPC sections 4.2, 4.4, 4.7, and 4.8<br>PL sections 2, 4<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>▪ HCP educational material<br>▪ PAC<br>▪ Controlled distribution program | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Event follow-up questionnaire<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| CRS | **Routine risk minimization measures**:<br>SmPC sections 4.2, 4.4 and 4.8<br>PL sections 2, 4<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>▪ HCP educational material<br>▪ PAC<br>▪ Controlled distribution program | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Event follow-up questionnaire<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| Cytopenias including aplastic anemia | **Routine risk minimization measures**:<br>SmPC sections 4.4 and 4.8<br>PL sections: 2, 4<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036 |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | | ZUMA-6: 31 Aug 2033 |
| Infections | **Routine risk minimization measures**:<br>SmPC sections 4.2, 4.4 and 4.8<br>PL sections: 2, 4<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| Hypogammaglobulinemia | **Routine risk minimization measures**:<br>SmPC sections 4.4 and 4.8<br>PL section: 4<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| **Important potential risk(s)** | | |
| Secondary malignancy | **Routine risk minimization measures**:<br>SmPC sections 4.4<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Event follow-up questionnaire<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| Immunogenicity | **Routine risk minimization measures**:<br>SmPC sections 4.8 | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Additional pharmacovigilance activities**:<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| RCR | **Routine risk minimization measures**:<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| TLS | **Routine risk minimization measures**:<br>SmPC sections 4.4<br>PL section 2<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| Aggravation of GvHD | **Routine risk minimization measures**:<br>SmPC section 4.4<br>PL section 2<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036 |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | | ZUMA-6: 31 Aug 2033 |
| Transmission of infectious agents via product | **Routine risk minimization measures**:<br>SmPC Sections 4.2<br>PL Section 3<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>None |
| Decrease in viability of the product due to inappropriate preparation of infusion | **Routine risk minimization measures**:<br>SmPC Sections 4.2<br><br>**Additional risk minimization measures**:<br>Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>None |
| CD19 negative relapse | **Routine risk minimization measures**:<br>None<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Event follow-up questionnaire<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| CAR T Persistence in relapsed patients | **Routine risk minimization measures**:<br>None<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>Event follow-up questionnaire<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| Failure to produce a viable CAR T cell product | **Routine risk minimization measures**:<br>None<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| **Missing information** | | |
| Use in pregnancy and lactation | **Routine risk minimization measures**:<br>SmPC sections 4.6<br>PL section 2<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040 |
| Use in non-Caucasian patient populations | **Routine risk minimization measures**:<br>None<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| New occurrence or exacerbation of an autoimmune disorder | **Routine risk minimization measures**:<br>SmPC section 5.1<br>Use restricted to physicians experienced in the treatment of hematological cancers | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None |

| Safety Concern | Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| | **Additional risk minimization measures**:<br>None | **Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |
| Long term safety | **Routine risk minimization measures**:<br>Use restricted to physicians experienced in the treatment of hematological cancers<br><br>**Additional risk minimization measures**:<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br>None<br><br>**Additional pharmacovigilance activities**:<br>KT-EU-471-0117: 14 Nov 2040<br>ZUMA-1: 31 Oct 2032<br>ZUMA-5: 30 Apr 2036<br>ZUMA-6: 31 Aug 2033 |

The MAH updated the overview of additional risk minimisation activity with regards to the prescriber survey (KT-EU-471-0116) which aims to evaluate the effectiveness of HCP educational material study. Final results of this study were submitted in June 2021 (EMEA/H/C/004480/II/0040) and this procedure is still ongoing. Tentatively, pending the final outcome of this procedure, the information added to the RMP is considered acceptable.

With regards to the controlled distribution programme, the MAH updated the table with data from the registry PASS (KT-EU-471-0117) concerning CRS, which is acknowledged.

### *Overall conclusions on risk minimisation measures*

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

### *Elements for a public summary of the RMP*

Part VI, summary of the risk management plan has been updated to include the new indication. The updates made in RMP Parts I through IV have been correctly reflected in the RMP summary.

## *2.8. Update of the Product information*

As a consequence of the extended indication, sections 4.1, 4.8, 5.1. and 5.2.of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The MAH also took the opportunity to amend the product information with minor editorial changes.

### 2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the addition of the adult r/r DLBCL and HGBL indication to the currently approved PIL has not introduced significant changes to the text or layout.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Diffuse large B cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

### 3.1.2. Available therapies and unmet medical need

The current standard of care for the first-line treatment of DLBCL is R CHOP, which results in 5 year and 10-year EFS rates of 47% and 35%, respectively, and 5-year and 10 year OS rates of 58% and 44%, respectively in patients 60 to 80 years of age. For patients 18 to 60 years of age treated with R-CHOP, 3-year EFS and OS rates are 79% and 93%, respectively. The optimal therapy for the first-line treatment of patients with HGBL has not been established, and there is no consensus whether regimens more intensive than R-CHOP are required; 4 year OS rates of 54.5% and 49.6% have been reported for R-EPOCH and R-CHOP, respectively.
Standard second-line therapy in the curative setting for LBCL is comprised of rituximab and platinum-containing salvage chemoimmunotherapy followed by HDT and auto-SCT for those who are eligible. The efficacy of this regimen has not been fully assessed for HGBL. While HDT auto SCT has curative potential, only half of patients respond to second-line salvage chemotherapy and are able to proceed to auto SCT, and poor outcomes are observed for patients who cannot undergo auto-SCT. Besides chemoresistant disease, other reasons for patients not being eligible to receive second line therapy include failure to mobilize CD34+ stem cells for auto SCT, poor performance status, organ dysfunction, comorbidities, unresolved treatment emergent toxicities, or older age. For patients who receive second-line therapy, outcomes are particularly poor for those with primary refractory disease or early relapse after first-line therapies and for patients with higher sAAIPI scores.
More recently, 2 therapies (polatuzumab vedotin and tafasitamab) were approved for transplant ineligible patients with r/r DLBCL, and although these new treatment options offer incremental improvements in response rates, duration of responses remain suboptimal and neither therapy has demonstrated curative outcome. Thus, a need remains for alternative second line therapies with curative intent, including those with a mechanism of action independent of chemotherapy sensitivity.

### 3.1.3. Main clinical studies

ZUMA-7 is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus SOCT in adult subjects with r/r LBCL.

## *3.2. Favourable effects*

EFS (stratified HR 0.398, 95%CI 0.308, 0.514), ORR and CR data are considered favourable and indicate a superior efficacy of axicabtagene ciloleucel as a second-line therapy in adult subjects with r/r LBCL compared with SOCT.

The risk of an EFS event for subjects in the axicabtagene ciloleucel arm was significantly reduced compared with the SOCT arm. Median EFS time was 6.3 months longer in the axicabtagene ciloleucel arm compared with the SOCT arm. The KM estimated event-free rate was higher for axicabtagene ciloleucel relative to SOCT. Treatment with axicabtagene ciloleucel resulted in a significant improvement in ORR compared with SOCT. The CR rate was 2-fold higher (65% vs 32%) in the axicabtagene ciloleucel arm compared with the SOCT arm.

## *3.3. Uncertainties and limitations about favourable effects*

Issues in the conduct of study result in uncertainties regarding the derived effects: measures such as a firewall to fully blind the study team in charge with the conduct of study where not appropriately pre-specified and hence decisions to alter the study might have been potentially made in the light of the accrued data. Modifications to the (interim) analysis plan for OS (multiple changes to the timing and number of interim analyses, changes and contradictions in the approach to control for multiplicity) add uncertainty and potentially render the type 1 error control for OS questionable.

EFS estimates might be biased in favour of axicabtagene ciloleucel. It is acknowledged, however, that this does not impact the derivation and interpretation of OS, and should not impact EFS to an extend which would render the benefit questionable. An additional limitation is the immaturity of the OS data.

While there are a number of CD19 negative patients who benefitted from axicabtagene ciloleucel axicabtagene ciloleucel therapy, a clear-cut and definite superiority of axicabtagene ciloleucel vs. SOCT cannot be established in CD19 patients, moreover, outcome data in CD19- patients are inferior to the outcomes found in CD19 positive patients. The data are less reliable due to the lower patient numbers, yet these tendencies are clearly observable.

## *3.4. Unfavourable effects*

Unfavourable effects of axicabtagene ciloleucel are the generally known identified risks, which are CRS, neurotoxicity and hematotoxicity. Comparing both treatment arms in ZUMA-7, the following observations were made for the axicabtagene ciloleucel arm compared to the SOC-arm:

- Higher incidence of hypogammaglobulinemia any grade
- Higher incidence of infections any grade
- Higher incidence of laboratory abnormalities any grade
- Higher incidence of cardiac symptoms any grade (sinus tachycardia, possibly associated with CRS)

## 3.5. Uncertainties and limitations about unfavourable effects

Generally, the spectrum of the unfavourable effects of axicabtagene ciloleucel as a CAR T cell product is known, and currently no major additional issues seem to arise. The disadvantage and limitation, respectively, is that the MAH applies for an indication extension with a rather limited follow-up time (DCO of 18 March 2021: median follow-up of 19.6 months for subjects treated with axicabtagene ciloleucel), which revealed some uncertainties.

## 3.6. Effects Table

**Table 28. Effects Table for axicabtagene ciloleucel (ZUMA-7 data cut-off: 18 March 2021)**

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Median EFS time | CA | months (95% CI) | 8.3 (4.5, 15.8) | 2.0 (1.6, 2.8) | Strength: Mature data and strong effect; Uncertainty: Only surrogate endpoint, biased estimate | |
| CR rate | CA | % (95% CI) | 65 (57.6, 71.9) | 32 (25.6, 39.8) | | |
| **Unfavourable Effects** | | | | | | |
| Neurotoxicity | Encephalopathy any grade | % | 49 | 8 | Strong evidence for relationship to axicabtagene ciloleucel (CRES) | |
| CRS | ≥ Grade 3 | % | 6 | 0 | Strong evidence for relationship to axicabtagene ciloleucel | |
| Prolonged cytopenia | ≥ Grade 3 | % | 29 | 60 | Strong evidence for relationship to axicabtagene ciloleucel | |
| Infections | ≥ Grade 3 | % | 14 | 11 | | |
| Deaths | | % (n) | 38 (64) | 46 (78) | | |

Abbreviations: CA (central assessment), CR (complete response), CRS (cytokine release syndrome), EFS (event-free survival), PD( progressive disease), TEAES (treatment-emergent adverse events)

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The strength of the findings is given by the fact that the proposed new indication is based on a trial first of its kind in the field of CAR-T cells: a randomized trial comparing axicabtagene ciloleucel versus SOCT in adult subjects with r/r LBCL. The proposed indication is supported by the data obtained in the ZUMA-7 study: ZUMA-7 demonstrated superior efficacy of axicabtagene ciloleucel as a second-line therapy in adult subjects with r/r LBCL compared with SOCT. The observed superiority based on EFS, ORR, CR rates indicate that clinically meaningful benefit could be achieved in a second line therapy setting in the intended population of patients with r/r LBCL. The safety profile of axicabtagene ciloleucel as second-line treatment in the intended target population appears acceptable, no new safety concerns have been identified. Overall, the TEAEs and risks are similar to what has been described for other CAR T cell therapies and for axicabtagene ciloleucel in the other indications, and are manageable with the current risk minimization measures presented in the SmPC.

The proposed new indication introduced with this extension includes HGBL. The WHO classifications from 2016/ 2022 indicate HGBL as an independent entity within the LBCLs. Inclusion of both DLBCL and HGBL subtypes as disease entities are supported by the efficacy data, and mechanism of action based on the expression of CD19. Importantly, the sample size of patients enrolled in the ZUMA-7 trial diagnosed with HGBL (HGBL: 43 pts, 24%; DLBCL: 110 pts, 61%) was considered sufficient to support the inclusion of this indication.

The new extension of indication contains a limitation to patients relapsing within 12 months from completion of first-line chemoimmunotherapy. Indeed, patients with late relapses eligible for standard of care and higher chance of definitive treatment with HDT-ASCT have not been enrolled. An extrapolation for later relapsing patients was not supported: while indirect comparisons for EFS and OS are difficult to interpret, the ORR of 88% with salvage chemotherapy (CORAL data) in later relapsing patients is similar to the ORR of 83% with Yescarta in early relapsing patients indicating comparable antitumour activity. In order to accommodate the study cohort and the sought indication, the MAH modified the indication to contain the 12 months limit, which was endorsed.

In the ZUMA-7 study, HDT + auto-SCT were parts of the treatment protocol in the control arm for patients intended to proceed to HDT-auto-SCT if there was a response to second-line therapy. Even though transplant eligibility was not specifically addressed as criterion for axicabtagene ciloleucel treatment eligibility it is likely that investigators only selected patients for the trial that could also be eligible for the SOCT arm. Thus, patients not eligible for HDT/SCT were not part of the trial population. From an efficacy point of view, it is acceptable to extrapolate the result from the trial to the population that was not included. Since safety has been established in later line settings that also included more advanced and likely more fragile patients extrapolation of safety is also accepted. Furthermore, there are not clearly defined criteria for transplant eligibility that could be used for defining the target population.

Some CD19 IHC negative patients seem to have benefitted from axicabtagene ciloleucel therapy, but a definite superiority of axicabtagene ciloleucel vs. SOCT cannot be established for CD19 IHC negative patients. On the other hand, data indicate that the outcome in CD19-negative patients may be worse compared to CD19-positive patients. However, due to the low patient numbers a substantial uncertainty on the efficacy in CD 19-negative patients remains. These findings would point to sensitivity issues of the IHC detection method, also known in the literature. Still, literature data clearly show that quantitative antigen density in LBCL assessed by flow cytometry correlates with outcomes after axicabtagene ciloleucel therapy. It is clear that further measures are required to address CD19 negativity in the future.

The current ESMO guideline on DLBCL diagnosis (published in Ann Oncol (2015) 26 (suppl 5): v116-v125.) states that: "A morphological diagnosis of DLBCL should be confirmed in all cases by immunophenotypic investigations, either immunohistochemistry (IHC) or flow cytometry or a combination of both techniques". The MAH implemented/committed to two measures, which were considered sufficient to address these aspects, as indicated under Section 3.7.3. below.

### 3.7.2. Balance of benefits and risks

Benefit indicated by the data appear to outweigh the observed unfavourable effects, at least in the majority of the patients.

### 3.7.3. Additional considerations on the benefit-risk balance

Appropriate wording was added in the SmPC section 4.4 indicating that potential risks and benefits associated with treatment of CD19-negative patients with Yescarta should be considered. Additionally, the MAH committed to further study the correlation of axicabtagene ciloleucel efficacy and CD19 expression profile, as assessed by flow cytometry and IHC at the time of relapse, by performing a dedicated interventional trial.

## *3.8. Conclusions*

The overall B/R of axicabtagene ciloleucel for treatment of r/r DLBCL and HGBL in adult subjects as second-line treatment is considered positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CAT considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of indication to include treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) for Yescarta; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the product information with minor editorial changes.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

### *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

### *Similarity with authorised orphan medicinal products*

The CAT and CHMP by consensus is of the opinion that Yescarta is not similar to Kymriah, Minjuvi, Polivy within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

### *Additional market protection*

Furthermore, the CAT has not considered the claim for additional market protection since an additional year of market protection was already granted as part of a previous variation (Yescarta II/42).

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Yescarta-II-46'