22 June 2018
EMA/481168/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

YESCARTA

International non-proprietary name: axicabtagene ciloleucel

Procedure No. EMEA/H/C/004480/0000

Note

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

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Table of contents

List of abbreviations

ABC	Activated B cell
ADR	Adverse drug reaction
AE	Adverse event
ALL	Acute lymphoblastic leukemia
APV	Aseptic process validation
ASCT	Autologous stem cell transplant
AUC	Area under the plasma concentration vs time curve
BSA	bovine serum albumin
CAR	Chimeric antigen receptor
CAT	Committee for Advanced Therapies
CBC	Complete blood count
CCR7	Chemokine receptor 7
CD3	Cluster of differentiation 3
CFR	Code of Federal Regulations
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
Cmax	Maximum observed plasma concentration
CNS	Central nervous system
CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine release syndrome
DHAP	Dexamethasone high-dose cytarabine cisplatin
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DOR	Duration of response
DORR	Duration of retreatment response
DP	drug product
DS	drug substance
DSMB	Data safety monitoring board
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalogram

ELISA	Enzyme-linked immunosorbent assay
EOP	End of production
FBS	Fetal bovine serum
FL	Follicular lymphoma
GALV	gibbon ape leukemia virus
GM-CSF	Granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
HC-DNA	host cell DNA
HCL	Hairy cell leukemia
HCP	host cell protein
HSA	Human serum albumin
IA1	Interim analysis 1
IA2	Interim analysis 2
ICH	International Conference on Harmonisation
ID	Identification
IFN	Interferon
IFN-γ	Interferon-gamma
IL	Interleukin
IL-1ra	Interleukin-1 receptor antagonist
IL-2R	Interleukin-2 receptor
IL-2Rα	Interleukin-2 receptor alpha
IPI	International prognostic indicator
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITAMs	Immunoreceptor tyrosine-based activation motifs
IWG	International Working Group
KTE-C19	Company code for axicabtagene ciloleucel (autologous T cells transduced with anti-CD19 chimeric antigen receptor; the investigational product)
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
LTFU	Long-term follow-up
LTRs	Long terminal repeats
mAb	Monoclonal antibody
MAS	Macrophage activating syndrome
MCB	Master cell bank
MCL	Mantle cell lymphoma

MIP	Macrophage inflammatory protein
mITT	Modified intend-to-treat
MOI	Multiplicity of infection
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ND	Not done
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
PVAC	process validation acceptance criteria
qPCR	Quantitative polymerase chain reaction
R-CHOP	Rituximab cyclophosphamide doxorubicin vincristine prednisolone
RCR	Replication-competent retrovirus
rIL	Recombinant interleukin
rIL-2	Recombinant IL-2
SAE	Serious adverse event
SAP	Statistical analysis plan
scFv	Single chain variable fragment
SCHOLAR-1	Retrospective, Patient-level, Pooled Analysis in Refractory Aggressive NHL
SD	Stable disease
sFASL	Soluble FAS ligand
SIN	self-inactivating
TBI	Total body irradiation
TCR	T-cell receptor
TD	Transduced
TFL	Transformed follicular lymphoma
Tnaïve	Percent naive memory phenotype
TNF	Tumour necrosis factor

TNF-α	Tumour necrosis factor-alpha
TRS	Tumour lysis syndrome
TU	transducing units
ULN	Upper limit of normal
US	United States of America
UT	Untransduced
VCN	Vector copy number
WBC	White blood cell
WCB	Working cell bank
WHO	World Health Organization
ZUMA-1	Study KTE-C19-101

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Kite Pharma EU B.V. submitted on 29 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for YESCARTA, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

YESCARTA was designated as an orphan medicinal product EU/3/14/1393 on 16 December 2014 in the following condition: Diffuse Large B-cell Lymphoma (DLBCL)

YESCARTA was designated as an orphan medicinal product EU/ 3/15/1553 on 09 October 2015 in the following condition: Primary Mediastinal B-Cell Lymphoma (PMBCL)

YESCARTA was designated as an orphan medicinal product EU/3/15/1579 on 11 November 2015 in the following condition: Follicular Lymphoma (FL)

Yescarta was granted eligibility to PRIME on 26 May 2016 in the following indication: Treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) who have not responded to their prior therapy, or have had disease progression after autologous stem cell transplant (ASCT).

Eligibility to PRIME was granted at the time in view of the following:

- DLBCL is a chronically debilitating and life-threatening condition. Refractory/relapsed DLBCL is a major cause of morbidity and mortality with a median survival of around 6 months and new treatment options would be welcomed.
- Although limited, the available nonclinical data supported the pharmacological rationale.
- From a clinical perspective, limited but promising results have been provided with 5 responders out of 7 patients at Month 1 in the ZUMA-1 study and 63% ORR in patients with DLBCL or PMBCL in the NCI study.
- Despite many uncertainties, KTE-C19 (Yescarta) could bring a major therapeutic advantage over existing therapies and consequently be of major public health interest.

The applicant applied for the following indication:

YESCARTA is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL) who are ineligible for autologous stem cell transplant (ASCT). Clinical experience indicates a significant improvement in overall response rate, including durable complete response (no evidence of disease), durable partial response, and survival compared to historical outcomes.

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. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004480/human_med_0

02292.jsp)

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0237/2017 on the agreement of a paediatric investigation plan (PIP) and on the granting of a partial waiver.

At the time of submission of the application, the PIP P/0237/2017 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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance axicabtagene ciloleucel contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific recommendation on Classification

The applicant Kite Pharma EU B.V. submitted on 28 April 2015 an application for scientific recommendation on Classification to the European Medicines Agency (EMA) for YESCARTA, which was designated as an Advanced Therapy Medicinal Product on 29 June 2015.

PRIME support

Upon granting of eligibility to PRIME, the Rapporteur was appointed by the CHMP.

A kick-off meeting was subsequently organised with the EMA, Rapporteur, assessor teams and experts from

relevant scientific committees. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures: Validation of transportation and plans to demonstrate comparability between manufacturing processes, EU batch release, discussion related to the risk of insertional mutagenesis, regulatory strategy and paediatric investigation plan.

Protocol assistance

The applicant received Scientific Advice on the development relevant for the proposed indications from the CHMP on 23 July 2015, 17 December 2015, 23 February 2017, and 14 September 2017. The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- Manufacturing process, definition of starting material, potency assay for release testing and release specification, Replication-Competent Retrovirus testing, testing and release strategy for cell banks, sterility testing, comparability following manufacturing changes, stability programme and shelf life, process validation for the retroviral vector.
- Completeness of the overall non-clinical programme, considering lack of relevant non-clinical models. Insertional mutagenesis evaluation.
- An open-label, non-comparative phase 1/2 study: Definition of the target population (DLBCL, PMBCL, and TFL) and existence of an unmet medical need. Whether a certain improvement in objective response rate and duration of response is considered clinically meaningful in comparison to historical data. Statistical testing in different cohorts of aggressive B-cell NHL. The proposed safety exposure from the clinical programme.
- A randomised, open label pivotal phase 3 study with standard of care therapy as comparator: Proposed study population (relapsed/refractory DLBCL) and definition. Event Free Survival as primary endpoint, its definition, and its appropriateness to show clinical benefit in second-line DLBCL. Key secondary endpoints (objective response rate and overall survival). Representativeness for European patients of the standard of care treatment in the control group. The modality and frequency of imaging and tumour assessment method. Statistical testing plan for primary and key secondary endpoints, including interim analysis. Reporting of serious adverse events. Proposed safety monitoring plan including replication competent retrovirus, cytokine levels, and immunogenicity.

1.2. Steps taken for the assessment of the product

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

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

The application was received by the EMA on	29 July 2017
Accelerated Assessment procedure was agreed-upon by CAT and CHMP on	22 June 2017
The procedure started on	17 August 2017
The CAT agreed to consult the national competent authorities on the environmental risk assessment of the GMO as the ATMP is a gene	10 November 2017

therapy medicinal product. The consultation procedure started on	
The Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	8 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	10 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 November 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2017
The CAT agreed on the consolidated List of Questions during the meeting on	08 December 2017
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The Procedure reverted to a standard timetable as agreed-upon by CHMP on:	14 December 2017
The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
- A GCP inspection at one clinical investigator site and one Sponsor site in the US were conducted during November-December 2017. The outcome of the inspection carried out was issued on	25 January 2018
- A GMP inspection of a manufacturing site for the active substance in the US, was carried out on 22-26 September 2017.The outcome of the inspection carried out was issued on - A GMP inspection of a manufacturer of the active substance intermediate in the US, was carried out on 20-21 September 2017. The outcome of the inspection carried out was issued on	23 November 2017 23 November 2017
The applicant submitted the responses to the CAT consolidated List of Questions on	19 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	29 March 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 April 2018
The CAT agreed on the consolidated List of Outstanding Issues during the meeting on	20 April 2018
The CAT agreed on a list of outstanding issues to be sent to the	26 April 2018

applicant on	
The applicant submitted the responses to the CAT List of Outstanding Issues on	23 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	08 June 2018
The consultation procedure related to the evaluation of the environmental risk assessment of the GMO closed on	11 June 2018
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to YESCARTA on	22 June 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to YESCARTA on	28 June 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Non–Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. NK/T-cell lymphomas are very rare. More than 60 specific NHL subtypes have been identified and assigned names by the World Health Organization (WHO). NHL subtypes are categorized by the characteristics of the lymphoma cells, including their appearance, the presence of proteins on the surface of the cells and their genetic features.

Aggressive lymphomas account for about 60 percent of all NHL cases. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL subtype. Primary mediastinal B-cell lymphoma (PMBL) is a subtype of large B-cell lymphoma that is putatively derived from a thymic B cell. Its clinical and molecular characteristics are distinct from other subtypes of DLBCL and, in fact, closely resemble those of nodular sclerosing Hodgkin lymphoma (NSHL). Transformation of follicular lymphoma (FL) is a morphological diagnosis based on the demonstration of diffuse large B-cell lymphoma (DLBCL) in a patient who has been diagnosed as having follicular lymphoma, either consecutively or concurrently.

2.1.2. Epidemiology

Data from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute (SEER) showed that NHL is the most prevalent haematological malignancy and is the seventh most common new cancer among men and women, accounting for 4% of all new cancer cases and 3% of cancer-related deaths

(Howlader et al, 2015). For 2016, SEER estimated 72580 new cases of NHL and 20150 deaths due to NHL in the United States (Howlader et al, 2015).

DLBCL is the most common type of NHL, accounting for 30–40% of all cases. DLBCL accounts for approximately 31% of all NHLs in Western countries and 37% of B-cell tumours worldwide. The median age at presentation is 70 years old; however, it can occur at any age, with a slightly higher incidence in men. The incidence rate of DLBCL was 3.44/100000 in the European Union (EU) in 2014 (RARECARENet 2017). The probability of having DLBCL increases with age, from 0.13% and 0.09% before the age of 29 to 1.77% and 1.4% after the age of 70 in men and women, respectively. For the vast majority of patients, the aetiology of DLBCL is unknown. Factors thought to potentially confer increased risk include immunosuppression (including AIDS, and iatrogenic aetiologies in the setting of transplantation or autoimmune diseases), ultraviolet radiation, pesticides, hair dyes, and diet. A subset of diffuse large B cell lymphoma, including immunoblastic and primary CNS disease is highly associated with the EBV virus, although unlike certain indolent histologies, the concept of antigen-driven lymphomagenesis is less developed in DLBCL.PMBCL constitutes approximately 2 % to 4 % of all non-Hodgkin lymphomas (around 6 % of diffuse large B-cell lymphomas (DLBCL). This disease affects mainly young adults (median age of 35), predominantly women (female/male ratio 1.7-2/1). There are also cases of PMBCL among children and adolescents. No risk factors for this type of lymphoma have been identified.

2.1.3. Biologic features, aetiology and pathogenesis

Initially, the classification of non-Hodgkin lymphoma was based on morphology, but advances in immunology and molecular medicine allowed the introduction of a biological classification for these diseases. DLBCL arises from mature B-cells at different stages of differentiation. Several gene mutations promote changes in B-cells, changing the gene expression and promoting a neoplastic transformation. During B lymphocyte ontogeny, after leaving the bone marrow, those cells travel to secondary lymphoid tissues where they will find their respective antigens promoting the development of secondary follicles. An antigen-dependent phase of B-cell development occurs at this site. In the germinal center of the secondary follicle, these lymphocytes are transformed into centroblasts that have a high rate of proliferation, while frequent and continuous somatic mutations of genes of the immunoglobulin variable chain occur, promoting maturation and differentiation into centrocytes and subsequently into plasma cells or in memory B-cells. Multiple lesions involving molecular pathways of B-cell proliferation and differentiation may result in the activation of oncogenes such as the BCL2, BCL6, and MYC genes and the inactivation of tumour suppressor genes such as p53 and INK4, as well as other important transcription factors such as OCT-1 and OCT-2.

The human CD19 antigen is a 95 kd transmembrane glycoprotein belonging to the immunoglobulin superfamily. CD19 is classified as a type I transmembrane protein, with a single transmembrane domain, a cytoplasmic C-terminus, and extracellular N-terminus. CD19 is a biomarker for normal and neoplastic B cells, as well as follicular dendritic cells. CD19 is critically involved in establishing intrinsic B cell signaling thresholds through modulating both B cell receptor-dependent and independent signalling. CD19 functions as the dominant signalling component of a multimolecular complex on the surface of mature B cells, alongside complement receptor CD21, and the tetraspanin membrane protein CD81 (TAPA-1), as well as CD225.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The clinical manifestations of diffuse large cell lymphomas are variable and depend on the site of disease involvement. These tumours have a rapid growth rate and present as masses, causing symptoms when they

infiltrate tissues or obstruct organs. Pain in an enlarged lymph node or organ may be noted if the lymphomatous mass enlarges rapidly. As with other types of non-Hodgkin lymphoma (NHL), diffuse large cell lymphomas can present with B-symptoms, including fever, drenching night sweats, and weight loss. Generalized pruritus may also be present.

Other symptoms can include the following: anorexia, pedal oedema (caused by extensive pelvic lymphadenopathy), fatigue, discomfort or shortness of breath (caused by mediastinal lymphadenopathy).

The diagnosis of DLBCL should be carried out in a reference haematopathology laboratory with expertise in morphological interpretation and the facilities to carry out the full range of phenotypic and molecular investigations.

A surgical excision biopsy remains the optimal method of diagnosis. This allows assessment of nodal architecture and provides adequate material for phenotypic and molecular studies. Ideally, the biopsy should be sent unfixed to the laboratory to allow flow cytometric studies to be carried out and high-quality DNA and RNA to be extracted.

DLBCL shows an aggressive behaviour with a median survival of less than 1 year in untreated patients.

Follicular lymphoma that transformed to diffuse large B-cell lymphoma (DLBCL) portend a poor prognosis for most patients, with a median overall survival (OS) of 1 to 2 years.

Outcomes for patients with relapsed/refractory aggressive B-cell NHL are poor. Only 10% of patients with relapsed/refractory disease will have long-term survival, and long-term benefit is generally limited to patients with chemotherapy-sensitive disease who achieve a response to second line platinum-based therapy and are able to proceed to autologous stem cell transplant (ASCT). Patients with refractory disease, defined as no response to last line of therapy or early relapse after ASCT, have low response rates to subsequent therapy and short overall survival (OS). Published reports have demonstrated response rates ranging from 0% to 23%, and in 1 study, median OS was less than 10 months for such patients (Philip et al, 1995; Moskowitz et al, 1999; Ardeshna et al, 2005; Seshadri et al, 2008; Hitz et al, 2010; Telio et al, 2012; Matasar et al, 2013). Similarly poor outcomes are observed for patients who have relapsed disease, but are ineligible for ASCT for a variety of reasons, such as inadequate response to second line therapy, relapse after second or greater line of therapy, failure to mobilize stem cells, or presence of comorbidities (Crump et al, 2004; Feugier et al, 2005; Colosia et al, 2014; Van Den Neste E et al, 2016).

2.1.5. Management

The current standard of care for first-line treatment for aggressive B-cell NHL is a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in combination with an anti-CD20 monoclonal antibody (mAb) such as rituximab (Flowers et al, 2010). Although more effective than chemotherapy alone, first-line R-CHOP only results in long term disease remission in < 40% of subjects. Thus, patients with relapsed or refractory aggressive B-cell DLBCL and PMBCL may comprise 60% or more of all subjects with aggressive B-cell NHL.

Patients with relapsed or refractory DLBCL and PMBCL typically are treated with a rituximab and platinum-based chemotherapy regimen, followed by ASCT for those who are eligible (Philip et al, 1995; NCCN, 2014; Tilly et al, 2015). However, studies in relapsed/refractory B-cell NHL indicate that only half of patients who respond to second-line therapy are able to proceed to ASCT (Philip et al, 1995; Moskowitz et al, 1999; Gisselbrecht et al, 2012; Crump et al, 2014). Thus, only a small fraction of patients with relapse/refractory

disease benefit from ASCT. Friedberg and colleagues have estimated that only 10% of all patients with relapsed/refractory disease will have long term survival following ASCT in the rituximab era (Friedberg, 2011). Outcomes are particularly poor for patients who have primary refractory disease after first-line therapies with or without rituximab; 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 disease range from 0 to 23% (Philip et al, 1995; Josting et al, 2000; Ardeshna et al, 2005; Telio et al, 2012; Matasar et al, 2013; Hitz et al, 2015), and primary refractory disease was found to be a significant risk factor for failing second-line therapy (Moskowitz et al, 1999). Outcomes are also poor for subjects with aggressive B-cell NHL that is refractory to second-line therapy (ORR of 18%) (Seshadri et al, 2008) or third-line therapy (ORR of 14%) (Ardeshna et al, 2005) .

Most patients with PMBCL will initially respond to therapy with a rapid decrease in the tumour mass, but rapid disease progression during treatment cycles is not uncommon. Second-line treatment strategies are like those used for DLBCL, attempting re-induction with non-cross-resistant agents, followed by consolidation with HDT-ASCT in those with a chemo-sensitive disease. In general, the outcomes of these patients have been disappointing (Sehn et al, 1998; Kuruvilla et al, 2008). The broad use of rituximab in first-line therapy has made recurrence less frequent, but harder to manage successfully (Gisselbrecht et al, 2010). Further, as described in Section 3.4, an analysis by the sponsor shows that historically, outcomes for patients relapsed/refractory aggressive NHL are similar, regardless of disease subtype.

Early relapse after ASCT, defined as relapse occurring ≤ 12 months after ASCT, has been found to be an adverse prognostic factor for survival in patients with aggressive B-cell NHL. In an analysis of data from the PARMA trial, the ORR to subsequent therapy was 40% for those with an early relapse and 69% for those with relapse more than 12 months after ASCT ($P < 0.0001$), and 8-year overall survival (OS) rates were 13% and 29% ($P < 0.0001$) for the 2 subsets (Guglielmi et al, 1998). Similarly, in the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL), 4-year event-free survival for patients who had early relapse after ASCT was significantly lower than that of subjects who relapsed more than 12 months after ASCT (46% v 56%; $p < 0.05$) (Gisselbrecht et al, 2012). Similarly, Nagle and colleagues (Nagle et al, 2013), reported a significantly shorter median OS for patients who had early relapse after ASCT than for those who relapsed ≥ 12 months after ASCT (8.2 vs. 26.7 month; $P = 0.01$).

Poor outcomes also are observed for patients with relapsed/refractory aggressive B-cell NHL who respond to salvage therapy, but are ineligible for transplant based on one or more factors, such as age > 65 years, inadequate response or early relapse after salvage therapy, relapse after second or greater line of therapy, failure to mobilize stem cells for ASCT, or presence of comorbidities or unresolved toxicities. A review of small, single-arm studies showed a median OS ranged from 4 to 13 months for patients with transplant-ineligible relapsed/refractory DLBCL (Colosia et al, 2014). In the CORAL trial, 129 of 193 patients who received third-line therapy, but did not undergo subsequent transplant (transplant ineligible), had worse survival than patients who underwent ASCT or allogeneic SCT (34/193 subjects): median survival was 3.3 months vs 11.1 months, respectively, and 2-year OS was 9.3% vs. 33.9%, respectively (Van Den Neste E et al, 2016). In the Groupe d'Etude des Lymphomes de l'Adulte LNH98-5 study of elderly patients with DLBCL, 77 of 202 patients treated with R-CHOP as first-line therapy experienced a relapse and did not undergo transplant; 2-year OS for this group was 26% (Feugier et al, 2005). In a National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) Phase 2 study of second-line therapy, 17 elderly patients who were not considered eligible for transplant had a median survival of 8.9 months (Crump et al, 2004). Although the CORAL study included a small group of patients who underwent ASCT or allogeneic SCT without achieving a response to third-line therapy, National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2014) and European Society for Medical Oncology (ESMO) guidelines (Tilly et al, 2012) suggest that patients who

relapse after second-line therapy are unlikely to respond to subsequent therapy and therefore generally are not eligible for ASCT.

According to current ESMO guidelines, clinical trials with novel drugs remain acceptable treatment options for subjects with relapsed/refractory DLBCL or PMBCL who are ineligible for ASCT due to chemo-refractory disease or other causes (Tilly et al, 2015; Vitolo et al, 2016). Treatment of relapsed/refractory TFL is not addressed in either the 2015 or 2016 ESMO guidelines, as treatment would proceed according to the transformed phenotype (in this case, DLBCL) (Wagner-Johnston et al, 2015).

Thus, the data from the literature indicate that under the current treatment paradigm, where virtually all patients will receive rituximab and an anthracycline as first-line therapy, those who are refractory to any line of therapy, those who are not eligible to proceed to transplant after relapse, and those who relapse early after transplant have uniformly low survival rates and no curative options.

Collectively, patients with relapsed/refractory aggressive B-cell NHL who are ineligible for ASCT have no curative options. No therapies are approved in this setting, and both National Comprehensive Cancer Network (NCCN) and European Society Medical Oncology (ESMO) guidelines indicate that there is a clear unmet medical need that warrants novel treatment strategies for these patients (NCCN, 2014; Tilly et al, 2015; Vitolo et al, 2016).

About the product

Axicabtagene ciloleucel is an engineered autologous T-cell immunotherapy product whereby a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction using an MSCV-based retroviral vector to express a CAR comprising an anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. CD19 is expressed as a surface antigen in DLBCL and other aggressive B-cell lymphomas. The transduced anti-CD19 CAR T cells are expanded ex vivo and infused back into the patient, where they can recognize and eliminate CD19 expressing target cells.

Axicabtagene ciloleucel binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19 expressing target cells.

The indication of the marketing authorisation application (MAA) for Yescarta was initially proposed for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL) who are ineligible for autologous stem cell transplant (ASCT).

The indication agreed at the CAT is for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy.

YESCARTA is intended, for autologous use only.

A single dose of YESCARTA contains 2×10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL suspension in an infusion bag.

Type of application and aspects on development

The CAT and CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the availability of preliminary underlying data to support the claim that the product has the potential to bring a therapeutic advantage in r/r DLBCL, PMBCL and TFL patients ineligible for ASCT. In this regard, the use of the proposed targeted cell therapy was considered to be a major therapeutic innovation.

However, during assessment the CAT concluded that it was no longer appropriate to maintain the accelerated assessment procedure as the evaluation of the dossier was no longer compatible with the previously agreed timetable. The reason for this is attributable to the adoption of a substantial list of questions, including major objections and the need for a GCP inspection during the course of the procedure. Subsequently, the assessment of the application reverted to a standard timetable.

2.2. Quality aspects

2.2.1. Introduction

YESCARTA (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare YESCARTA, patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19-expressing target cells.

Each patient specific single infusion bag of YESCARTA contains a suspension of anti-CD19 CAR T cells, strength 0.4×10^8 - 2×10^8 cells in approximately 68 mL.

YESCARTA is presented as a clear to opaque, white to red dispersion of cells for infusion formulated with Cryostor CS10 (5% dimethylsulfoxyde (DMSO)), sodium chloride and human serum albumin.

YESCARTA is supplied in an ethylene-vinyl acetate cryostorage bag individually packed in a shipping cassette.

2.2.2. Active Substance

Axicabtagene ciloleucel is produced from leukapheresis material obtained from individual patients, and therefore the product is unique to each patient. The patient's T cells are engineered *ex vivo* to express the anti-CD19 CAR using a replication incompetent γ-retroviral vector containing the CAR transgene.

The section on the active substance is separated into two parts; part 1 for the gene therapy retroviral vector PG13-CD19-H3 and part 2 for the transduced cells resulting in the active substance axicabtagene ciloleucel.

The entire manufacturing process is covered by respective GMP certificates.

Part 1 - Retroviral vector PG13-CD19-H3

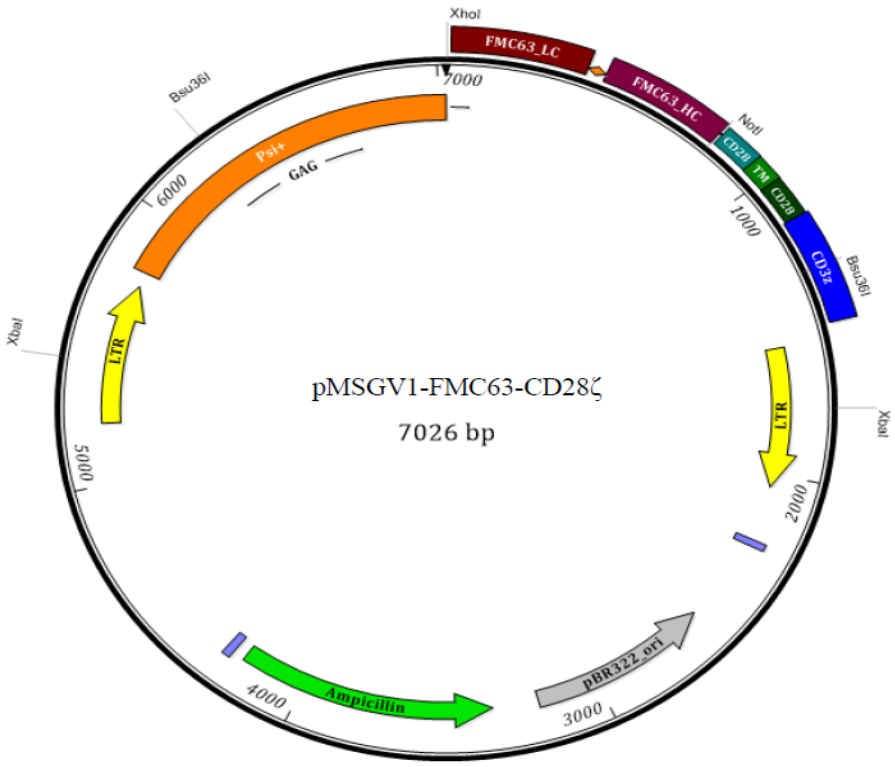
General information (retroviral vector PG13-CD19-H3)

The retroviral vector PG13-CD19-H3 is a murine stem cell virus (MSCV)-based vector pseudotyped with the gibbon ape leukemia virus (GaLV) envelope.

The MSCV vector is a long terminal repeat (LTR)-driven non-self-inactivating (SIN) retroviral vector that encompasses the 5'LTR (also promoter for transgene expression), a packaging signal including the splice donor and splice acceptor sites, the FMC63-based (anti-CD19 FMC63-CD28-CD3ζ) CAR sequence containing a human GM-CSF receptor signal peptide, FMC63 light chain variable region, linker peptide, FMC63 heavy chain variable region, CD28 (hinge, transmembrane and cytoplasmic region), and CD3ζ (cytoplasmic region), followed by the MSCV 3'LTR (Figure 1).

Transfer of genetic material into T cells occurs via retroviral transduction of autologous T cells. The manufacturing of the vector is based on a stable packaging cell clone PG13-CD19-H3 from which a Master Cell bank (MCB)/Working Cell Bank (WCB) system has been established.

Figure 1 – Elements of the retroviral transfer



Manufacture, process controls and characterisation (retroviral vector PG13-CD19-H3)

Manufacturing process (retroviral vector PG13-CD19-H3)

The applicant provided an adequate description of the vector manufacturing process. This includes the description of the manufacturing process steps, flow-charts and description of the IPCs and operating ranges and/or acceptance limits.

The PG13-CD19-H3 vector is produced constitutively from a stably-transduced PG13 (ATCC CRL-10686™) cell line. For production of retroviral vector under GMP, cells from a single vial of WCB are expanded and the culture supernatant is harvested, filtered and filled into cryostorage bags.

Control of materials (retroviral vector PG13-CD19-H3)

The packaging cell clone is based on PG13 cells, a cell line that is commonly used to generate retroviral vector particles by introducing a γ-retroviral transfer vector of interest. These NIH3T3-derived cells stably express the Gibbon Ape Leukemia Virus (GALV) envelope and the Moloney murine leukemia virus (MoMLV) gag-pol proteins.

Stable, retroviral transfer of the PG13-CD19 transfer vector and subsequent selection of the cell clone PG13-CD19-H3 were conducted at the National Cancer Institute (NCI, Bethesda, Maryland, US). As the vector has the full 3'LTRs (and is no SIN-vector) the proviral DNA will have two functional LTRs, and due to cellular co-expression of the MoMLV gag-pol and the GALV envelope, vector particles are produced and constitutively released into the supernatant. Both cell banks are established under Good Manufacturing Practices (GMP). Overall the testing strategy and characterisation of the cell banks is considered adequate. The genetic stability of the WCB and end-of-production (EOP) has been investigated. The test method and results are adequately described. Genetic stability of the construct has been demonstrated.

Adequate information and acceptance criteria are given for all the listed ingredients.

The MCB was tested and released based on the ICH Q5A (R1) guideline. A single vial of the PG13-CD19-CAR-H3 MCB was used to produce 323 vials of WCB. The WCB has been shown to be free of bacterial, fungal and mycoplasma contamination in compliance with ICH Q5A (R1) and Ph. Eur. (5.2.3). The WCB was also found to be negative for replication-competent retrovirus.

Manufacturing process development and validation (retroviral vector PG13-CD19-H3)

An initial manufacturing process has been developed. Further adaptations were made, leading to the commercial process.

For process validation of the commercial manufacturing process three manufacturing runs have been conducted, two at small-scale and one at full-scale level using 15 CS10 cell stacks. The rationale and the provided data show that the manufacturing at small-scale is representative for the commercial large-scale run and considered acceptable.

In the manufacturing process of axicabtagene ciloleucel vector supernatant is used for the transduction of peripheral blood mononuclear cells (PBMCs). Sub-analyses of batches harvested show consistency within a campaign and within the batches manufactured according to the commercial manufacturing process with respect to titre and impurities levels.

As terminal sterilisation is inapplicable for the vector starting material, aseptic manufacturing was validated with successfully completed process simulation runs and adequate requalification. Method suitability for the test on sterility (Ph. Eur. 2.6.1, direct inoculation), mycoplasmas (Ph. Eur. 2.6.7, culture and indicator cell culture assay) and endotoxin (Ph. Eur. 2.6.14, LAL) has been sufficiently clarified, demonstrating compliance with Ph. Eur. requirements.

The ongoing process verification (OPV) run by the applicant is endorsed. According to the applicant the actions to be taken in the event of control rule violations are defined in the OPV program.

Characterisation (PG13-CD19-H3 retroviral vector)

The characterisation of the PG13-CD19-H3 vector included both structure and function. The studies demonstrated that the PG13-CD19-H3 vector encodes the FMC63-CD28-CD3ζ transgene. Transduction results in integration of the vector genome into the genome of the T cells. The FMC63-CD28-CD3ζ transgene is

transcribed to RNA and translated to anti-CD19 CAR. Anti-CD19 CAR T cells bind to CD19 expressing cells. Upon engagement with CD19, T cells are activated and secrete IFN-γ. Detection of IFN-γ is considered an appropriate measure of functionality of the CAR construct.

Characterisation of PG13-CD19-H3 vector impurities was performed to evaluate process consistency among PG13-CD19-H3 vector lots. Specific components were evaluated in detail.

Impurities identified were host cell protein, HC-DNA, BSA and p30 protein. Each harvest of PG13-CD19-H3 vector is considered a unique lot, and testing is conducted to assure sterility, while safety tests for mycoplasma, *in vitro* virus and replication competent retrovirus (RCR) are performed only on material in the last harvest from the production campaign. The last harvest is considered a worst-case condition, and testing at this stage assures that the entire production campaign remains free of adventitious agents and that replication competent retrovirus is not present.

Specification (PG13-CD19-H3 retroviral vector)

The applicant provided a justification for the setting of specifications that is mainly based on manufacturing experience. Specifications cover appearance, identity, titer, activity and safety testing.

The PG13-CD19-H3 vector undergoes testing for adventitious agents prior to release for use in production of axicabtagene ciloleucel. The retroviral vector harvest is tested for adventitious viruses by *in vitro* assay and for replication competent viruses (RCR). All PG13-CD19-H3 vector lots tested to date have been negative for adventitious viruses and RCR. Study reports on the vector harvest testing were provided. In addition, the provided risk evaluation regarding potential generation of RCR during manufacture is acceptable. It is agreed that the occurrence of RCR in Yescarta is considered unlikely.

The analytical procedures used for release testing of PG13-CD19-H3 vector have been validated or verified as appropriate. Validations of the non-compendial analytical methods used to analyse PG13-CD19-H3 vector were performed in accordance with the ICH Q2(R1) guideline, Validation of Analytical Procedures: Text and Methodology. Verifications of the compendial analytical methods for Endotoxin, Mycoplasma, and Sterility testing of PG13-CD19-H3 vector were performed in accordance with guidance in ICH Q2(R1), the United States Pharmacopoeia (USP), and the European Pharmacopoeia (Ph. Eur.). All of these verifications showed no sample matrix interference effects, confirming that the methods are suitable for the testing of PG13-CD19-H3 Vector.

Summaries of the validations and verifications for each method are provided.

The analytical methods for PG13-CD19-H3 vector produce quantitative results. Batch analysis data are available for lots of PG13-CD19-H3 vector manufactured and released in accordance with current Good Manufacturing Practices.

Stability (PG13-CD19-H3 retroviral vector)

The stability of the PG13-CD19-H3 vector is being evaluated via long-term studies. In addition, the stability of PG13-CD19-H3 vector stored at either accelerated or stress (room temperature) conditions has been evaluated. All studies were conducted in accordance with ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products.

Long-term stability studies are ongoing with 8 lots of PG13-CD19-H3 vector stored at the recommended storage temperature. These studies are being conducted with lots used for clinical production, lots used for process validation and potential commercial production, and lots designated for commercial production. All of the PG13-CD19-H3 vector lots were manufactured by the commercial manufacturer.

PG13-CD19-H3 vector was exposed to elevated temperature to support potential temperature excursions that may occur during long term storage or during transportation.

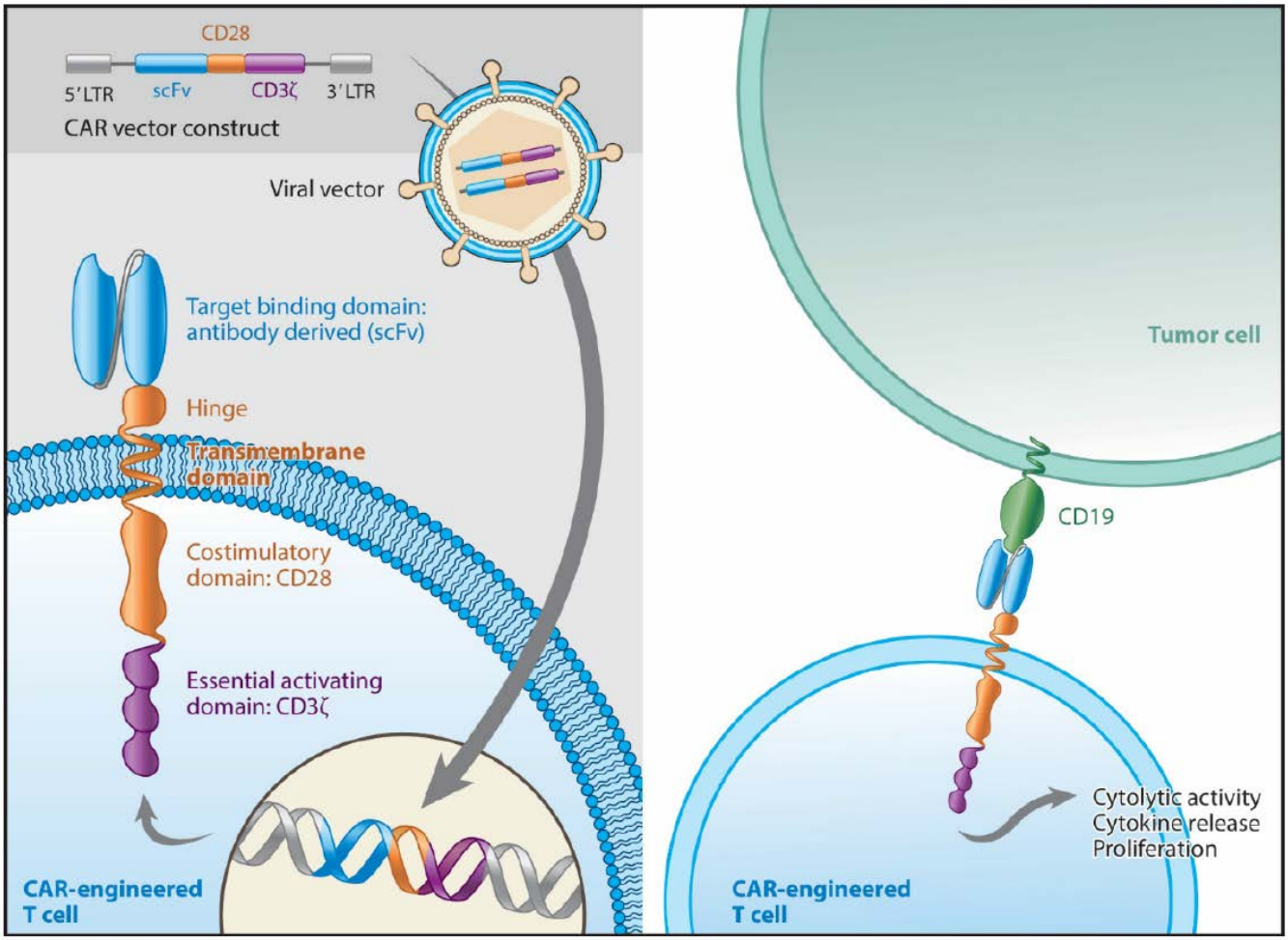
Stress testing was conducted on samples from. The objective of this testing was to evaluate the potential for several tests routinely performed as part of PG13-CD19-H3 vector stability studies to be stability indicating. As such, test results for each lot were trended against results obtained at time zero.

Part 2: axicabtagene ciloleucel

General information (axicabtagene ciloleucel)

The active substance consists of autologous T cells genetically modified *ex vivo* by transduction with a retroviral vector to express an anti-CD19 CD28/CD3ζ CAR to target CD19 on the cell surface of malignant B cells. The mechanism of action is shown in Figure 2.

Figure 2 – Axicabtagene ciloleucel CAR construct and mechanism of action



Manufacture, process controls and characterisation (axicabtagene ciloleucel)

Description of the manufacturing process and process controls (axicabtagene ciloleucel)

The manufacturing process of axicabtagene ciloleucel starts with apheresis collection from a patient. The applicant confirmed that apheresis for procurement of the cell starting material is performed in centres which have been authorised or licensed by the competent authorities and qualified by the applicant (Directive 2004/23/EC). A statement is included in the SmPC for healthcare professionals handling Yescarta to take appropriate precautions to avoid potential transmission of infectious diseases. It is further stated that throughout the manufacturing process, universal precautions are taken to avoid potential transmission of infectious diseases for all patients.

The next steps in the manufacturing process include lymphocyte enrichment, T-cell activation, retroviral transduction and T-cell expansion.

Description of the manufacturing process is very brief. However, for each step the process parameters, the proven acceptable range, the normal operating range or set point and the classification into critical and non-critical process parameters have been presented. The applicant established a control strategy within the manufacturing facility, which is considered acceptable.

Control of critical steps is based on performance parameters which have an impact on critical quality attributes are classified as critical.

Product traceability of axicabtagene ciloleucel from apheresis material to finished product is sufficiently described. The applicant maintains unique patient identifiers to ensure product traceability. This assures a patient's apheresis material is manufactured to Yescarta and the appropriate lot is returned to the patient. Information on the product label is verified upon receipt of each lot upon importation into Europe from the Kite manufacturing site in the US.

Control of materials (axicabtagene ciloleucel)

All establishments and personnel involved in cell procurement and testing of the apheresis material are qualified by a competent authority for the purpose of those activities. This includes also the use of CE-marked kits for respective donor testing.

The donor procurement and testing follow the national requirements of the member states where the product will be marketed, in line with Directive 2006/17/EC.

The applicant provided an overview of the reagents used in manufacturing of the active substance, the testing requirements and respective acceptance criteria as well as the intended use. For the latter one, measures are in place to ensure adequate quality for manufacturing of axicabtagene ciloleucel.

Several different types of disposable materials are used during manufacturing of axicabtagene ciloleucel. A summary of the results obtained from materials that were tested for extractables and potential leachables, including associated toxicology assessments, has been provided.

Five components of biological origin are used in the manufacture of axicabtagene ciloleucel including PG13-CD19-H3 vector (see above) and patient apheresis material.

Process validation (axicabtagene ciloleucel)

Overall, the commercial manufacturing process at Kite's facility (2355 Utah Avenue, El Segundo, CA90245 US) is considered validated.

Regarding microbiological safety, process performance qualification and process validation were successfully completed with all lots complying with microbiological release specifications. Aseptic process validation (APV) at has been thoroughly described demonstrating consideration of relevant APV interventions and adequate incubation conditions. All APV runs were successfully completed and post-incubation growth promotion demonstrated for tryptic soy broth.

Transport validation of the frozen PBMC from the EU site to the US site for further manufacturing has been demonstrated. Furthermore, the applicant confirms that commercial shipment will be performed with a temperature logger.

Traceability of the final product was established for all, with lots of final product sent from Kite Pharma, US, to Lonza Netherlands B.V. and then to a mock treatment center.

Manufacturing process development (axicabtagene ciloleucel)

History of process development has been described for the different manufacturing steps. For some steps different raw materials and parameters have been evaluated. Most of the development steps are sufficiently described and the chosen parameters and materials justified.

For process characterisation, a formal risk assessment has been performed and different steps of the process have been experimentally addressed by intentionally varying selected process parameters to identify critical process parameters (CPPs) for process consistency and product quality.

Development of other important process stages included analysis of apheresis starting material regarding use of different apheresis equipment, different apheresis storage temperatures and time and their impact on performance parameters at different stages during manufacturing. From the few batches tested, apheresis equipment and storage time within the set limits seem to have no impact on the analysed parameters.

Selected parameters for the cryopreservation step have been analysed and shown to be suitable.

Comparability

Data from comparability studies to support changes introduced during development were provided and are considered acceptable.

Characterisation (axicabtagene ciloleucel)

Product characterisation data supporting the mechanism of action of axicabtagene ciloleucel have been provided and include studies on integration of the CAR gene, CAR expression, antigen recognition and engagement, activation and release of cytokines, killing of target cells, cell composition and T-cell phenotypes as well as multiplicity of infection.

Characterisation studies are focusing on parameters determining the potency of the active substance.

Specification, analytical procedures, reference standards, batch analysis, and container closure (axicabtagene ciloleucel)

The manufacturing process for axicabtagene ciloleucel is a continuous process, and the transition from active substance to finished product does not include any hold steps, hence, specification, analytical procedures, validation of analytical procedures, batch analysis and justification of specifications, respectively are provided in the final product section. Considering the nature of the product, the applicant's approach is considered acceptable.

No release of active substance is performed.

Stability (axicabtagene ciloleucel)

As no hold step is foreseen at active substance level before manufacturing of finished product, no stability studies have been performed at that level. Data have been provided on the stability of the cryopreserved PBMCs which are considered to be an intermediate in active substance manufacturing.

Stability data collected to date confirmed that PBMC stored at the established storage condition are stable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Yescarta (axicabtagene ciloleucel final product) consists of autologous T cells that have been genetically modified *ex vivo* to express a chimeric antigen receptor to target CD19 on the cell surface of malignant B cells. The active substance of Yescarta, axicabtagene ciloleucel, is composed of a patient's T cells that have undergone *ex vivo* T-cell activation, gene transfer by replication-deficient retroviral vector (PG13-CD19-H3 vector), and expansion. These transduced T cells are then formulated in a cryopreservation medium suitable for infusion. Each final product bag of Yescarta is filled to deliver a target dose of 1.0 x 10^6 to 2.0 x 10^6 CAR positive viable T cells/kg of patient weight. Yescarta is supplied cryopreserved at a temperature of ≤ -150°C in cryostorage bags. The cryostorage bag contains a nominal volume of 68 mL of formulated axicabtagene ciloleucel final product. The composition of Yescarta (axicabtagene ciloleucel final product) consists of anti-CD19 CAR-T cells formulated with Cryostor CS10, sodium chloride and human albumin.

The active substance of Yescarta comprises CD3-positive T cells that have been transduced with an anti-CD19 CAR using a retroviral vector. The product may also contain a small percentage of autologous natural killer (NK) cells or cells with a phenotypic characteristic of NK T cells. B cells, monocytes and other white blood cells are present at very low levels.

Excipients used for the production of finished product are 0,9% sodium chloride injection which provides, albumin (human) which is a stabiliser and CryoStor CS10 agent.

A series of development studies were conducted to determine the optimal conditions for cryopreservation of Yescarta.

It was agreed that CryoStor is not regarded as a novel excipient.

The primary container closure system intended for distribution of Yescarta is CryoStore, commercially available, CE-marked ethylene vinyl acetate (EVA) cryostorage bag specifically designed for storage of blood and blood components.

The suitability of the primary container closure system has been shown based on results from extractable and leachable testing, container closure integrity testing, and long-term and accelerated stability studies.

The secondary packaging for Yescarta is an aluminium cassette, designed to protect the product during storage, shipment, and handling.

Manufacture of the product and process controls

Information regarding the manufacturer of Yescarta is provided.

The entire manufacturing process is covered by respective GMP certificates.

Each bag of Yescarta is filled to deliver a target dose of 1.0 x 10^6 to 2.0 x 10^6 CAR T cells/kg of patient weight in a nominal volume of 68 mL. The batch formula is equivalent to the composition of the final product.

The finished product manufacturing process is well described. The whole manufacturing process is continuous with transition from active substance to finished product without holding steps.

The commercial manufacturing process for Yescarta is essentially unchanged from the clinical manufacturing process. Flow diagram of the Yescarta manufacturing process is provided.

Yescarta is formulated with 0.9% sodium chloride (NaCl), human serum albumin (HSA), and CryoStor CS10 prior to the cryopreservation step.

Process validation has been addressed in the active substance part.

The final product is shipped to Lonza, NL frozen in a dry-vapor liquid-nitrogen shipper. A transport validation has been performed. A temperature monitoring device is included in each shipper.

Product specification

Since the manufacturing process from receipt of the apheresis starting material through to finished product is continuous and no active substance is isolated, it is considered acceptable that only specifications for the finished product has been provided. Product specification includes control of identity, purity and impurities, potency (including cell viability and anti-CD19 CAR expression) and other general tests.

The analytical methods, the unique identification numbers and the corresponding pre-set acceptance criteria have been provided.

The analytical methods in the finished product part have been described and are adequately validated. Summary of method validation parameters and corresponding results have been provided. All method validations met the acceptance criteria set in the corresponding validation protocols. Validation information demonstrating that the compendial and non-compendial analytical procedures used to test finished product are suitable for their intended purpose is presented.

Batch analyses are provided for lots of Yescarta that were manufactured at the proposed commercial site.

The applicant justifies omission of repeated release testing in the EU by referencing to point 11.17 of Part IV - GMP requirements for Advanced Therapy Medicinal Products of EudraLex Volume 4.

Stability of the product

The applicant's formal stability program includes lots of Yescarta held at recommended and/or accelerated storage conditions.

Based on the provided data, the applicant's proposed shelf life of 12 months at -150^{0}C is accepted.

The stability of Yescarta upon completion of thawing is up to 3 hours at room temperature (20°C to 25°C). A post-thaw hold time up to 3 hours was shown to not result in altered.

Adventitious agents

TSE compliance

Raw materials of animal or human origin are used in the production of Yescarta. Compliance with the TSE guideline has been demonstrated for raw materials used for vector production and cell banking by providing

valid EDQM certificates of suitability. Human serum albumin (HSA) is used as excipient. It is a marketed product in Europe with reference to an E.U. plasma master file (EMEA/H/PMF/000008/05/II/017/G). All other reagents used during vector production and T-cell transduction are in compliance with the TSE guideline (EMA/410/01 rev.3). The donors of the T cells are of autologous origin and therefore the TSE risk is not relevant. In summary, compliance of animal-derived materials with the current TSE-guideline and compliance of the human-derived material with E.U. or U.S. TSE relevant regulations is demonstrated and supported by respective certificates.

Virus safety

Due to the nature of the product, the manufacturing process of the PG13-CD19-H3 vector and of the Yescarta finished product does not contain any step that removes or inactivates viruses. In addition, the final finished product is not tested for adventitious viruses. Control of adventitious agents is mainly based on selection and testing of starting materials and raw materials of biological origin and testing of the retroviral vector. In order to ensure safety of the product, procedural controls are followed for acceptance of material used in the manufacture of PG13-CD19-H3 vector and axicabtagene ciloleucel. These controls are as follows:

1. Safety testing of the PG13-CD19-CAR-H3 master cell bank and PG13-CD19-CAR-H3 working cell bank
2. Procedural controls, raw material controls, and safety testing of the PG13-CD19-H3 vector
3. Media and reagents used in the manufacturing of Yescarta are sourced from qualified vendors

This strategy is considered acceptable.

Virus safety of Yescarta is sufficiently shown.

GMO

The GMO are autologous T-cells genetically modified with a non-SIN retroviral vector based on MSCV pseudotyped with the GALV envelope protein and encoding the CAR consisting of a CD19-specific scFv and the CD28/CD3-zeta costimulatory domains under control of the MSCV 5´LTR enhancer/promoter region.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

A major objection was identified during the procedure and was related to the fact that consistency of transduction of the autologous cells had not been fully demonstrated.

On the basis of the comprehensive responses and clarification provided by the applicant, together with various commitments, the issue was considered resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Yescarta is considered acceptable. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

The CHMP endorsed the CAT assessment regarding the conclusions on the chemical, pharmaceutical and

biological aspects as described above.

2.2.6. Recommendations for future quality development

In the context of the obligation of the applicant to take due account of technical and scientific progress, several points for investigation, including the manufacturing process and control of the product, were recommended.

The CHMP endorsed the CAT assessment regarding the recommendations for future quality development.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant provided *in vitro* and *in vivo* non-clinical pharmacology data for KTE-C19. For *in vitro* evaluation of specific activity against $CD19^+$ target cells, the Applicant used CD19 CAR T cells from patients that were enrolled in clinical trials conducted by the National Cancer Institute (NCI). Single-dose toxicology studies in animals were not performed by the Applicant due to the lack of a relevant animal model. Instead, evaluation of potential on-target/off-tumour activity has been included into a non-GLP primary pharmacology study using anti-murine CD19 CAR T cells as a surrogate for studies of the human anti-CD19 CAR T cell product.

Data on the comparability of anti-CD19 CAR T-cell product manufactured by the CLP-1.0 process and the CLP-2.0 process were submitted.

The pharmacological studies submitted were either literature publications or non-GLP studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Comparability between NCI and Kite Products

The manufacturing process of the CD19 CAR T cells from patients with melanoma (CLP-1.0) differed from the manufacturing process of the CD19 CAR T cells patients with advanced B-cell haematologic malignancies (CLP-2.0). Differences were as follows: in CLP-2.0, T cells were stimulated, transduced and expanded in closed bags using serum-free media and harvested after 6 to 8 days in culture, then cryopreserved prior to use. The CLP-2.0 process is similar to the CLP-2.2 process used for KTE-C19, but CLP-2.2

The comparability of anti-CD19 CAR T-cell product manufactured by the CLP-1.0 process and the CLP-2.0 process was demonstrated through split apheresis studies at NCI, which showed a lower transduction efficiency of the CLP-2.0 process as compared to the CLP-1.0 process (37.1 ± 6.1% compared with 78.4 ± 5.4%, respectively), while total cell numbers, fold expansion, the INF-γ release upon co-culture with $CD19^+$ target cells, and the phenotypic evaluation was similar. Products prepared by the CLP-2.0 process (NCI) and the CLP-2.2 process (Kite) were compared directly using split apheresis products from 4 subjects. These studies demonstrated statistically equivalent transduction efficiency for the NCI CLP-2.0 product and KTE-C19, and similarity for in-process parameters (wash step yield, percent viability on Day 2, Day 3, and at

harvest; and fold expansion), potency (ie, level of IFN-γ produced upon co-culture of anti-CD19 CAR T cells with CD19+ target cells) and cell growth profiles.

CD19 Expression Profile Summary

Targeting B-lineage haematologic malignancies via CD19 is based on earlier findings demonstrating that expression of CD19 is restricted to cells, both normal and malignant, of the B-lineage. Early publications by Nadler and colleagues (Nadler et al, 1983; Anderson et al, 1984) showed that CD19 protein is expressed on all B-lineage lymphoid cells, from the pro-B-cell maturation stage to naïve and differentiated B cells. Uckun and colleagues (Uckun et al, 1988) confirmed and extended these findings by demonstrating that leukemic progenitor B cells also express CD19, and that erythroid, myeloid, megakaryocytoid, and multilineage normal bone marrow progenitor cells do not express CD19. More recently, Johnson and colleagues (Johnson et al, 2009) showed that primary lymphoma cells from patients with diffuse large B-cell lymphoma (DLBCL) expressed CD19, whereas reference T cells did not. Olejniczak and colleagues (Olejniczak et al, 2006) examined the expression pattern and levels of CD19 in peripheral blood, bone marrow, and lymph node tissue from patients with 6 different common B-cell malignancies (CLL, small lymphocytic lymphoma [SLL], B-lineage acute lymphoblastic leukemia [ALL], hairy cell leukemia [HCL], DLBCL, and follicular lymphoma [FL]). Nearly all samples within each type were considered positive for CD19. Expression levels of CD19 were variable across the different B-cell malignancies, but all B-cell malignancies examined showed consistently measurable levels of CD19 expression above reference $CD3^+$ T cells. In summary, evidence from key published literature demonstrates that CD19 is expressed on the surface of normal B-lineage cells as well as most B-cell malignancies, including DLBCL and FL, two subtypes of non-Hodgkin lymphoma (NHL). Other investigators have shown that CD19 is also expressed in primary mediastinal B-cell lymphoma (PMBCL) (Rodriguez et al, 1994) and mantle cell lymphoma (MCL) (Leonard et al, 2001).

In Vitro

Characterization of Human Anti-CD19 CAR T Cells

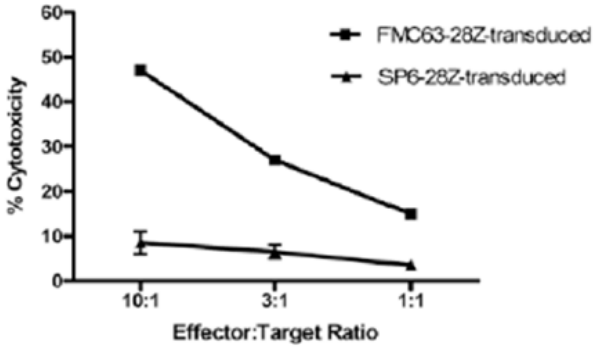
Initial *in vitro* characterization studies were performed using anti-CD19 CAR-transduced T cells, generated using T cells from patients with melanoma. The anti-CD19 CAR-transduced T cells were generated at NCI using the CLP-1.0 process.

The specificity and potency of the anti-CD19 CAR T cells were evaluated by measuring their ability to produce IFN-γ in response to co-culture with either $CD19^+$ or $CD19^-$ target cells. For each experiment, transduced T cells were cultured overnight with target cells and IFN-γ secreted into the media was measured using an enzyme-linked immunosorbent assay (ELISA). Results showed that production of cytokines by anti-CD19 CAR T cells was dependent on both the presence of the anti-CD19 CAR T cells and the co-culture with $CD19^+$ target cells. For control cultures containing either transduced or nontransduced T cells co-cultured with CD19- target cells or no target cells, only minimal cytokine production was observed.

The characteristics and specificity of the T cells transduced with the anti-CD19 CAR construct were further assessed by comparing phenotype, scFv expression and cytokine induction using K562 cells (a cell line derived from a patient with chronic myeloid leukemia) engineered to express either CD19 or, as a negative control, the low affinity human nerve growth factor receptor (CD19-K562 and NGFR-K562, respectively). Results from these experiments demonstrated that $CD3^+$ T cells expressed the anti-CD19 CAR and both $CD3^+CD4^+$ and $CD3^+CD8^+$ cells produced IFN-γ in a CAR- and CD19-specific manner. The percentage of $CD3^+$

T cells ($CD4^+$ and $CD8^+$) that produced IFN-γ in response to a $CD19^+$ target (54%) was generally consistent with the percentage of $CD3^+$ T cells that expressed the FMC63 scFv (ie, 45%, the transduction efficiency). Biological activity of the anti-CD19 CAR T cells was also tested in a cytotoxicity assay. Control T cells were transduced with a CAR construct (SP6-28Z), analogous to FMC6328-Z, but specific for hapten 2, 4, 6-trinitrobenzenesulfonic acid. Results demonstrated that T cells transduced with FMC63-28Z killed primary CLL cells in a dose-dependent and CD19-specific manner, while the T cells transduced with SP6-28Z did not.

Figure 1 Cytotoxicity of anti-CD19 CAR T cells



Cytotoxicity is reported as the mean +/- the SEM of duplicate determinations. This experiment is representative of three similar experiments that used cells from 3 different donors. FMC63-28Z is the anti-CD19 CAR construct; SP6-28Z is the hapten-specific negative control CAR construct.

Additional characterization studies were performed to analyze the composition (percent transduction and phenotype), specificity, and biological activity of autologous anti-CD19 CAR T cells derived from 15 subjects with advanced NHL enrolled in NCI Protocol 09-C-0082 investigating anti-CD19 CAR T cells for the treatment of patients with advanced B-cell haematologic malignancies. The anti-CD19 CAR-transduced T cells were generated at NCI using the CLP-2.0 process.

Product composition was determined by immunophenotypic analysis of surface markers (CD3, CD4, CD8 and CD45RA) by flow cytometry. The markers CCR7 and CD45RA are broadly utilized to distinguish between naïve ($CCR7^+CD45RA^+$), central memory ($CCR7^+CD45RA^-$), effector memory ($CCR7^-CD45RA^-$) and effector ($CCR7^-CD45RA^+$) human T-cell subsets. Phenotyping assays showed that the anti-CD19 CAR T cells derived from these subjects with advanced NHL comprised both $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells. Furthermore, the transduced T cells primarily comprised central memory T cells (T_{cm}) and effector memory T cells (T_{em}), as defined by CCR7/CD45RA surface expression.

Specificity, potency, and poly-functionality of the anti-CD19 CAR T cells derived from the 15 subjects with advanced NHL were further evaluated utilizing Luminex™ to measure cytokines produced during co-culture with CD19-K562 or NGFR-K562 (negative control) target cell lines. A panel of 17 different cytokines, chemokines, and effector molecules with various immunomodulatory roles was measured in co-cultures of anti-CD19 CAR T cells and target cells.

The 17 analytes comprised the following: IL-2 as a marker of immune cell homeostasis and proliferation; IL-6, IL-13, tumour necrosis factor-α (TNF-α), and granulocyte macrophage-colony stimulating factor (GM-CSF) as markers of pro-inflammatory activity; IL-4, IL-5, IL-10, IFN-γ, and soluble CD137 as markers of immune-

modulating activity; macrophage inflammatory protein (MIP)-1α and MIP-1β as chemokines; and granzyme A, granzyme B, soluble FAS ligand (sFASL), soluble FAS (receptor for sFASL), and perforin as effector molecules. All subject-derived anti-CD19 CAR T-cell products produced IFN-γ when incubated with CD19-K562 target cells, consistent with the *in vitro* data (Kochenderfer et al, 2009). Induction of all 17 analytes occurred in a CD19-dependent manner. These data demonstrate that anti-CD19 CAR T-cell products generated from multiple donors all exhibit CD19-dependent activation, and the capacity to produce diverse biological factors in response to CAR stimulation.

Characterization of an Anti-Murine CD19 CAR Construct Analogous to KTE-C19

Since the anti-CD19 scFv utilized for KTE-C19 does only recognize human CD19, a murine surrogate was engineered for non-clinical proof-of-concept studies in immune competent mice. This surrogate model used an anti-murine CD19 CAR construct that was similar to KTE-C19 with the exception of the scFv, which has been derived from the 1D3 mAb recognizing murine CD19. Murine T cells were transduced with the anti-murine CD19 CAR construct and adoptively transferred into syngeneic mice challenged with a CD19-expressing 38c13 lymphoma cell line to investigate the anti-lymphoma effect of the anti-murine CD19 CAR T cells.

In addition, the surrogate murine CD19 CAR T cells were investigated *in vitro* for CD19-specific activation by measuring INF-γ release in co-cultures of the anti-murine CD19 CAR T cells and $CD19^+$ and $CD19^-$ target cells. Thereby, the anti-murine CD19 CAR T cells also revealed some basal activity in the presence of $CD19^-$ cells as well as in the absence of any target cells. The basal activity became evident by a ~30-50 fold increase in IFN-γ release when comparing transduced T cells with untransduced cells in the control situations. Irrespective of this basal activity, a significant increase of secreted IFN-γ was still observed, when the CD19 CAR T cells were co-cultured with $CD19^+$ target cells. A similar basal activity was not observed with the anti-human CD19 CAR T cells.

In Vivo

Studies Using a Murine Model of Lymphoma and Anti-murine CD19 CAR T Cells

The administration of the anti-murine CD19 CAR T cells into the syngeneic mouse lymphoma model revealed both the ability of the CD19 CAR T cells to prevent establishment of a lymphoma and to eradicate already established lymphoma masses including metastasis. Administration of the anti-murine CD19 CAR T cells in both the prophylactic and the therapeutic setting resulted in prolonged survival of the mice while control animals became rapidly moribund due to lymphoma and were euthanized. Using the syngeneic mouse lymphoma model, the Applicant also investigated the influence of total body irradiation (TBI) prior to the administration of the lymphoma cells and the CD19 CAR T cells which revealed the importance of the TBI-induced lymphodepletion for prolonged survival of these animals and thus for a successful outcome of the CAR T cell therapy.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted.

Safety pharmacology programme

No safety pharmacology studies have been conducted.

Pharmacodynamic drug interactions

No formal pharmacodynamic drug interaction studies have been conducted.

2.3.3. Pharmacokinetics

Absorption

Absorption studies have not been performed as they are not relevant to this type of product.

Distribution

The persistence of the anti-murine CD19 CAR T cells was also evaluated in the syngeneic mouse lymphoma model using flow cytometry analysis.

The chosen model provides expansion, and survival of the CD19 CAR T cells (e.g. $CD19^+$ target tumour cells, endogenous cytokines, chemokines and cellular interactions of a fully functional immune system). The anti-murine CD19 CAR T cells could only be detected in spleen at Day 8, but no longer at Day 63 post-infusion (Kochenderfer et al., 2010a). Thus, persistence of CD19 CAR T cells could only be demonstrated for a short time period, despite a prolonged anti-lymphoma effect and B-cell aplasia which were evident for up to the 209 days (the latest time point investigated). Presence of anti-murine CD19 CAR T cells in spleen was investigated 8 days and 63 days post-infusion.

No other non-clinical pharmacokinetic analyses were performed.

Metabolism

The anticipated metabolic products of KTE-C19, a human autologous T-cell product, are typical cellular degradation products resulting from normal cellular clearance mechanisms (Erwig and Henson 2008).

Excretion

Elimination of T cells from the body is not regulated by excretion; rather by physiological processes such as T-cell apoptosis. Thus, standard excretion pharmacokinetic analysis techniques do not apply.

Pharmacokinetic drug interactions

Appropriate in vitro and in vivo models to assess potential pharmacokinetic drug interactions for KTE-C19, an autologous human T-cell product, do not exist. Possible impact of drugs used for management of cytokine release syndrome (e.g. by altering T cell function) is discussed in the context of clinical safety.

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicity studies have been conducted.

On-target/off-tumour toxicity of CD19 CAR T cells

On-target/off-tumour toxicity of CD19 CAR T cells in the syngeneic mouse lymphoma model, which has been evaluated during the pharmacology study in parallel with the anti-lymphoma effect and the persistence of the anti-murine CD19 CAR T cells. The observed prolonged depletion of normal B cells known to express CD19 confirmed the expected on-target/off-tumour effect of the CD19 CAR T cells on normal B cells. Additional toxicities of the anti-murine CD19 CAR T cells did not became evident in the pharmacology studies.

Repeat dose toxicity

No repeat-dose toxicity studies have been conducted (see non-clinical discussion).

Genotoxicity

No genotoxicity studies have been conducted (see non-clinical discussion).

The combination of both the use of a γ-retroviral vector with full-length viral LTRs and the high proliferative potential of the transduced T cells provides a certain risk of insertional oncogenesis. A detailed evaluation of published literature was provided that addressed the resistance of mature mouse T cells to transformation induced by genomic integration of γ-retroviral vectors. The clinical experience with administration of human T cells that were transduced with γ-retroviral vectors to either express the KTE-C19 CAR construct itself or other transgenes did so far not reveal cases of insertional oncogenesis.

These data implies a very low likelihood for T cell transformation induced by γ-retroviral insertional mutagenesis. Moreover, the high resistance of mouse T cells to cell transformation described by Newrzela et al indicates that this aspect can hardly be investigated in a mouse model.

Carcinogenicity

No carcinogenicity studies have been conducted (see non-clinical discussion).

Reproduction Toxicity

No reproductive toxicity studies have been conducted (see non-clinical discussion).

Toxicokinetic data

Not applicable.

Local tolerance

No local tolerance studies were conducted (see non-clinical discussion).

Other toxicity studies

No other toxicity studies were performed.

2.3.5. Ecotoxicity / environmental risk assessment

The environmental risk assessment was performed in accordance with Annex II to Directive 2001/18/EC on the deliberate release into environment of genetically modified organisms (GMOs) and following the precautionary principle using the methodology set down in Commission Decisions 2001/83/EC, 2002/812/EC, 2002/623/EC and EMA guidelines on environmental risk assessments for medicinal products consisting of, or containing GMOs (EMEA/CHMP/BWP/473191/2006) and on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006).

In accordance with Article 6 of Regulation (EC) No 726/2004, national competent authorities established under Directive 2001/18/EC have been consulted.

The ERA included as part of the submission of the MAA discusses the environmental risk assessment for the clinical use of YESCARTA. Potential risks for the environment associated with the clinical use of YESCARTA are generation and transmission of replication competent retroviruses (RCRs), transmission of residual infectious retroviral vector particles, or transmission of genetically modified T-cells. Since either the likelihood of these risks or the potential hazards have been evaluated to be negligible, the overall environmental risk has also been concluded as negligible. This conclusion has been supported during the consultation process.

2.3.6. Discussion on non-clinical aspects

Non-clinical *in vitro* pharmacology studies were performed with CD19 CAR T cells that were generated using two previous manufacturing processes established at the NCI (CLP-1.0 and CLP-2.0); neither of them represents the current process (CLP-2.2). It was agreed in the context of scientific advice that the non-clinical data generated with CD19 CAR T cells manufactured at NCI do not need to be repeated with CD19 CAR T cells manufactured using the current CLP-2.2 process provided that comparability and equivalent performance of the products derived from the different manufacturing processes can be demonstrated. Data from split apheresis studies performed at NCI were provided that compared the CLP-1.0 and the CLP-2.0 processes. Although these data revealed a lower transduction rate of the CLP-2.0 process (37.1 ± 6.1%) as compared to the CLP-1.0 process (78.4 ± 5.4%), the specific activity against $CD19^+$ target cells was not impaired as demonstrated by a comparable IFN-γ release upon co-culturing of CAR T cells and $CD19^+$ target cells. Since the percentage distribution of naïve, central memory, effector memory, and effector T cell subsets was comparable in both CD19 CAR T cell products. Although the potential reason for the lack of correlation between transduction efficiency and IFN-γ release when comparing CD19 CAR T cells manufactured with both processes was not clarified, it is not considered necessary to repeat the non-clinical *in vitro* data with KTE-C19 manufactured using the current CLP-2.2 process, since from a non-clinical point of view, comparability and/or equivalent performance has been sufficiently demonstrated between the products derived from the different processes. Moreover, IFN-γ release and cytotoxicity are also evaluated during manufacturing of KTE-C19 either for release of the final product (IFN-γ secretion) or during characterization studies (cytotoxicity).

Overall, the provided non-clinical *in vitro* data sufficiently demonstrate specific activity of KTE-C19 against its target antigen CD19. In addition, the immunophenotypic analysis of the anti-human CD19 CAR T cells suggests that both transduced $CD4^+$ and $CD8^+$ T cells are present in the final product. Percentage distributions of naïve, central memory, effector memory, and effector T cell subsets varied between different donors. Moreover, the Luminex™ analysis demonstrated that all 17 tested analytes were specifically released by the CD19 CAR T cells when co-cultured with $CD19^+$ target cells suggesting a certain poly-functionality of

the CAR T cells at the end of the manufacturing process. Although these data are rather considered as characterization data of the final product than non-clinical pharmacology data, they are still important as they support the versatile capability of KTE-C19 with regard to lymphocyte activation, proliferation, trafficking and effector mechanisms.

In addition to the *in vitro* evaluation of KTE-C19, a murine surrogate CD19 CAR T cells was established for *in vivo* evaluation in a syngeneic mouse lymphoma model. This approach provided important proof-of-concept for the overall design of the chosen CD19 CAR construct including for example the choice of the co-stimulatory domain. Such a surrogate model may also be considered as the most appropriate non-clinical model for investigating the persistence of the CD19 CAR T cells and for evaluating potential on-target/off-tumour effects of the CAR T cells. On the other hand, it is evident that crucial parameters of the CAR T cell may differ between the murine surrogate CD19 CAR T cells and the human CD19 CAR T cells. This includes for example the binding affinity of the scFv, the manufacturing of the transduced cells, the composition of T cell subsets, and the basal T cell activity which was observed in the murine surrogate only. Despite these expected differences, the use of murine surrogate CD19 CAR T cells in immunocompetent mice instead of testing KTE-C19 in immunocompromised mice is an acceptable approach that overcomes some of the limitations of the *in vivo* testing of KTE-C19 in immunocompromised animals, such as unspecific xenogeneic immune responses of KTE-C19 in mice or the lack of complex interactions of the CAR T cells with other components of the immune system. Since both models do have clear, although differing, limitations with regard to the translation of the non-clinical pharmacology data to human, additional non-clinical *in vivo* pharmacology data (e.g. testing of KTE-C19 in immunocompromised animals transplanted with human $CD19^+$ tumour cells) would not add significant value to the available non-clinical and clinical pharmacology data sets.

The provided non-clinical pharmacokinetic investigations focused on the *in vivo* persistence of the murine surrogate CAR T cells in the syngeneic mouse lymphoma model, which is acceptable for this type of product. The chosen model provides all necessary stimuli that are considered important for a specific activation, expansion, and survival of the CD19 CAR T cells (e.g. $CD19^+$ target tumour cells, endogenous cytokines, chemokines and cellular interactions of a fully functional immune system). Despite these ideal preconditions, the anti-murine CD19 CAR T cells could only be detected in spleen at Day 8, but no longer at Day 63 post-infusion (Kochenderfer et al., 2010a) probably CAR T cells may have persisted in tissues such as bone marrow, but remained undetectable by the method used; or despite limited persistence, CAR T cell engraftment was sufficient to eradicate lymphoma and induce long-lasting B-cell aplasia during the observation period in the animal model.

YESCARTA comprises engineered human T-cells, therefore there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for drug development were not performed.

Instead the on-target/off-tumour effect on normal B cells was confirmed during the pharmacology studies in the syngeneic mouse lymphoma model. This effect on normal B cells was expected based on the expression pattern of CD19 and resulting B cell aplasia has been observed in both the syngeneic mouse lymphoma model and in study participants that were treated with KTE-C19 in clinical trials. Other toxic effects of anti-murine CD19 CAR T cells were not evident in the mouse lymphoma model. However, off-target toxicities are also not expected to be reliably detected in the surrogate mouse model, since off-target recognition of other antigens may differ between the anti-human and anti-murine CD19 CAR T cells due to the different scFvs that were used in the CD19 CAR constructs. Similarly, the use of KTE-C19 in immunocompromised mice would also not be expected to reliably predict off-target effects, since potential differences of cross-recognition of unrelated antigens, differences of antigen expression patterns, and differences in the *in vivo*

survival, activation and expansion of KTE-C19 are expected to hamper detection of potential off-target effects in such a model.

In addition to the potential toxicities of the CD19 CAR T cells that are either dependent on the expression pattern of the chosen target antigen (on-target/off-tumour toxicities) or on the cross-reactivity of the chosen ScFv with other non-target antigens (off-target toxicities), there are also expected risk that are associated with the general mode of action of CAR T cells, such as uncontrolled T cell proliferation, tumour lysis syndrome (TRS), cytokine release syndrome (CRS) and macrophage activation syndrome (MAS). These toxic effects cannot be investigated in non-clinical studies as they are general effects of CAR T cells and the extent of expected toxicities are largely based on patient-specific parameters such as the individual tumour load.

No studies have been conducted to evaluate the effects of YESCARTA on fertility, reproduction and development. This is acceptable based on the type of product, the expression pattern of the target antigen and the lack of a relevant animal model. The risk of inadvertent germline transmission of the CD19 CAR construct has not been addressed; however, the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005) indicates that the risk of germline transmission associated with the administration of genetically modified human cells is considered to be low and, as animal testing of human cells may be difficult or not meaningful, non-clinical germline transmission studies of human genetically modified cells are not recommended.

It is not known if Yescarta has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Yescarta is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Assessment of immunoglobulin levels and B-cells in newborns of mothers treated with Yescarta should be considered. It is unknown whether it is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

No carcinogenicity or genotoxicity studies have been conducted with Yescarta. The combination of both the use of a γ-retroviral vector with full-length viral LTRs and the high proliferative potential of the transduced T cells provides a certain risk of insertional oncogenesis which has previously been addressed in a Scientific Advice procedure. Literature data reported an exceptionally high resistance of mature mouse T cells against transformation induced by genomic integration of γ-retroviral vectors. Moreover, there were no reported cases of insertional oncogenesis (see Clinical Safety) of either KTE-C19 itself or T cells that were transduced with γ-retroviral vectors encoding other transgenes – and that is reassuring. The experience so far with mouse and human T cells suggests that T cell transformation due to genomic integration of γ-retroviral vectors is, if at all, a very rare event.

No formal pharmacodynamic drug interaction studies have been conducted. KTE-C19 comprises human autologous cells transduced with a retroviral vector containing an anti-CD19 CAR. As such, appropriate in vitro and in vivo models to assess potential pharmacodynamic drug interactions do not exist. CYP enzymes and other classically described metabolic pathways are not involved in the metabolism of cellular therapy.

Potential risks for the environment associated with the clinical use of Yescarta are generation and transmission of replication competent retroviruses (RCRs), transmission of residual infectious retroviral vector particles, or transmission of genetically modified T-cells. From the environmental risk assessment it is concluded that these risks are negligible.

The CHMP endorsed the CAT discussion on the non-clinical aspects as described above.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical development package provided for KTE-C19 was limited due to the type of product and the limitations of animal models available for investigating pharmacodynamics, pharmacokinetics, and toxicity aspects of KTE-C19, but it was considered adequate. The presented non-clinical *in vitro* and *in vivo* data that address CD19 CAR expression on transduced T cells, specific activation of CD19 CAR T cells, the *in vivo* anti-lymphoma activity and persistence of the surrogate CD19 CAR T cells, and B cell aplasia as an expected on-target/off-tumour effect are considered sufficient.

The CHMP endorsed the CAT conclusions on the non clinical aspects as described above.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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.

Table 1: Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	KTE-C19-101 (ZUMA 1)	5.3.5.1	Phase 1: safety; Phase 2: efficacy measured by ORR; DOR, best overall response, PFS, OS	Open-label; multicenter	Axicabtagene ciloleucel; single infusion; target dose 2 × 10^6 cells/kg bw.	Phase 1: 8 leukapheresed; 7 treated Phase 2 : 111 leukapheresed 101 treated	Refractory DLBCL, PMBCL, and TFL (adults) Phase 1 All disease types Phase 2 Cohort 1: DLBCL- Cohort 2: PMBCL + TFL Cohort 3: refractory or relapsed transplant ineligible DLBCL, PMBCL, or TFL	Single infusion	Phase 1: complete Phase 2: Cohorts 1 and 2, enrollment and treatment complete; follow-up ongoing Cohort 3, enrollment ongoing
Safety and Efficacy	KTE-C19-102 (ZUMA 2)	2.7.4 Summary of Clinical Safety	Efficacy measured by ORR; DOR, best overall response, PFS, OS; safety and tolerability	Open-label; multicenter	Axicabtagene ciloleucel and KTE-C19 (XLP process); single infusion; target dose 2 × 10^6 cells/kg bw	[redacted]	Relapsed/ refractory MCL (adults)	Single infusion	Ongoing
Safety and Efficacy	KTE-C19-103 (ZUMA 3)	2.7.4 Summary of Clinical Safety	Phase 1: safety, DLT Phase 2: CR, DOR, MRD	Open-label; multicenter	KTE-C19 (XLP process); single infusion; target dose 1 to 2 × 10^6 cells/kg bw		Relapsed/ refractory adult ALL	Single infusion	Ongoing
Safety and Efficacy	KTE-C19-104 (ZUMA 4)	2.7.4 Summary of Clinical Safety	Phase 1: safety; DLT Phase 2: CR, DOR, MRD	Open-label; multicenter	KTE-C19 (XLP process); single infusion; target dose 2 × 10^6 cells/kg bw		Relapsed/ refractory pediatric ALL	Single infusion	Ongoing
Safety and Feasibility	NCI 09-C-0082[1]	5.3.5.1	Safety and feasibility, expansion and persistence of anti-CD19 CAR T cells, tumor response	Dose escalation; single center	NCI Anti-CD19 CAR T cells; single infusion; target dose 2 × 10^6 cells/kg bw in Cohorts 11, 13, and 14; 6 × 10^6 cells/kg bw in Cohort 12		Relapsed/ refractory NHL (DLBCL, PMBCL, TFL, FL, MCL) and CLL Cohorts 11 through 14 (N = 13)	Single infusion	Ongoing

Other planned or ongoing studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	KTE-C19-107 (ZUMA 7)	NA	Superiority vs SOC measured by EFS; efficacy vs SOC on PFS, OS, ORR, CR, DOR	Randomized; open label; multicenter, active-controlled	Axicabtagene ciloleucel; single infusion; target dose 2 × 10^6 cells/kg bw		Relapsed /refractory DLBCL (adults)	Single infusion	Planned

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report

Safety and Efficacy	KTE-C19-105 (ZUMA 5)	NA	Efficacy measured by ORR; PFS, best overall response, DOR, OS; safety	Open-label; multicenter	Axicabtagene ciloleucel; single infusion; target dose 2×10^6 cells/kg bw		Relapsed/ refractory indolent NHL	Single infusion	Planned
Safety and Efficacy	KTE-C19-106 (ZUMA 6)	NA	Phase 1: safety, DLT in combination with atezolizumab Phase 2: efficacy in combination with atezolizumab measured by CR; ORR, DOR, PFS, OS, safety	Open-label; multicenter; axicabtagene ciloleucel followed by atezolizumab	Axicabtagene ciloleucel; single infusion; target dose 2×10^6 cells/kg bw Atezolizumb 1200 mg Q3W		Refractory DLBCL (adults)	Single infusion	Ongoing

Abbreviations: ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DLT, dose limiting toxicity; DOR, duration of response; EFS, event-free survival; FL, follicular lymphoma; MCL, mantle cell lymphoma; MRD, minimum residual disease; NA, not applicable; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; SOC, standard of care; TFL, transformed follicular lymphoma. 1 Clinicaltrials.gov number NCT00924326.

It is noted that studies were ongoing and subject numbers quoted were accurate at the time of document preparation.

2.4.2. Pharmacokinetics

The pharmacology results are focused on data from patients treated in NCI 09-C-00082 and ZUMA-1 studies

NCI 09-C-0082:

The 13 subjects from this study comprise a group similar to the ZUMA-1 population with respect to disease characteristics (refractory DLBCL, PMBCL, or TFL), conditioning chemotherapy regimen received (low dose), anti-CD19 CAR T-cell characteristics (cryopreserved cells manufactured with the same retroviral vector and anti-CD19 construct), and target dose (2 x 10^6 anti-CD19 CAR T cells/kg for all subjects in ZUMA-1 and 6/7 subjects in NCI 09-C-0082).

Pharmacokinetics of anti-CD19 CAR T cells were assessed by means of measuring the presence, expansion, and persistence of anti-CD19 CAR T cells at approximately 7 days (+/-3), 14 days (+/-3), 4 weeks (± 2 weeks), 3 months (± 1 month), and 6 months (± 1 month) after cell infusion.

Serial blood samples were taken after cell infusion and subjected to a quantitative polymerase chain reaction (qPCR) test using a method developed at the NCI (Kochenderfer et al, 2015). The absolute number of persisting anti-CD19 CAR T cells per microliter (µL) of blood was based on the percentage of anti-CD19 CAR-expressing cells in the product as determined by flow cytometry (see supplemental methods of publications by Kochenderfer and colleagues [Kochenderfer et al, 2012; Kochenderfer et al, 2015]), with normalization to expression of the housekeeping gene β-actin and to the absolute number of mononuclear blood cells to derive a final value of CAR positive cells/µL of blood.

In the cohorts 11-14 with cryopreserved CAR-T cells used, all 13 evaluable subjects had measurable anti-CD19 CAR T-cells in blood at Day 7 and/or Day 14. Across all subjects, the median values at Days 7, 14, and 28 were 33 cells/µL, 13 cells/µL, and 1 cell/µL, respectively. The median peak value across all subjects (Cmax) was 86 cells/µL (range: 6 to 294 cells/µL). Due to the small sample size no correlation with efficacy and safety variables was conducted.

ZUMA-1 phase 1/2:

Anti-CD19 CAR T-cell levels were measured in the blood of subjects enrolled in Phase 2 Cohorts 1 and 2 combined. The presence, expansion, and persistence of anti-CD19 CAR T cells were monitored in blood by quantitative polymerase chain reaction (qPCR) analysis at various time points before and after infusion of axicabtagene ciloleucel. Similarly, levels of circulating cytokines were assessed at multiple time points before and after conditioning chemotherapy and infusion of axicabtagene ciloleucel. In addition, normal B-cell levels were evaluated in blood by flow cytometry to monitor the on-target and off-tumour effect of anti-CD19 CAR T cells.

Results of the primary analysis showed that anti-CD19 CAR T cells were measurable in peripheral blood within the first 14 days after the axicabtagene ciloleucel infusion in all evaluable subjects. Anti-CD19 CAR T cells exhibited an initial rapid expansion with a median time to peak level of anti-CD19 CAR T cells in blood of 8 days (range: 8.0 to 78.0 days, with one outlier) after axicabtagene ciloleucel infusion. The median peak level across all subjects (maximum observed plasma concentration [Cmax]) was 41.9 cells/µL (range: 0.8, 1513.7cells/µL). Levels of anti-CD19 CAR T cells decreased toward background levels by 3 months of the infusion (range: 0 to 15.8 cells/µL), but were measurable at the last assessment in most evaluable (i.e., responding) patients. The median area under the blood concentration vs time curve (AUC) from Day 0 to Day 28 (AUC0-28) was 462.3 cells/µL days.

Results were similar in the analysis performed at 12 months of follow-up. In overall, Peak levels of anti-CD19 CAR T cells occurred within the first 8-15 days after YESCARTA infusion. The median peak level of anti-CD19 CAR T cells in the blood (C_{max}) were 38.3 cells/µL (range: 0.8-1513.7 cells/µL), which decreased to a median of 2.1 cells/µL by 1 month (range: 0-167.4 cells/µL) and to a median of 0.4 cells/µL by 3 months (range 0-28.4 cells/µL) after YESCARTA infusion.

Dose proportionality and time dependencies

The number of anti-CD19 CAR T cells in blood was positively associated with objective response including both CR and PR. Subjects who had an objective response had higher levels (peak and AUC at 1 month) of anti-CD19 CAR T cells compared to non-responders. Levels of anti-CD19 CAR T cells were not assessed after disease progression, which limits the ability to correlate long-term cell persistence and DOR. The median peak anti-CD19 peak levels in responders (n=55) were 4 times higher than the corresponding level in non-responders (n= 28)(45.6 cells/µL vs 11.4 cells/µL). Median AUC levels in subjects with CR or PR were 5 times higher than the corresponding level in non-responders (562.0 days*cells/µL vs. 103.3 days*cells/µL,).

Higher peak levels of anti-CD19 CAR T-cell levels were found to be associated with the occurrence of neurologic events, but not with CRS.

Pharmacokinteic correlations were similar for response according to the central assesment. The number of anti-CD19 CAR T cells in blood was positively associated with objective response (CR or PR). The median anti-CD19 CAR T cell C_{max} levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/µL vs 21.2 cells/µL). Median $AUC_{Day\ 0\ -\ 28}$ in responding patients

(n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days × cells/µL vs. 222.0 days × cells/µL).

Figure 2 : Peak Number of CAR T Cells in Blood (/uL) by Best Response (Phase 2) mITT Analysis Set.

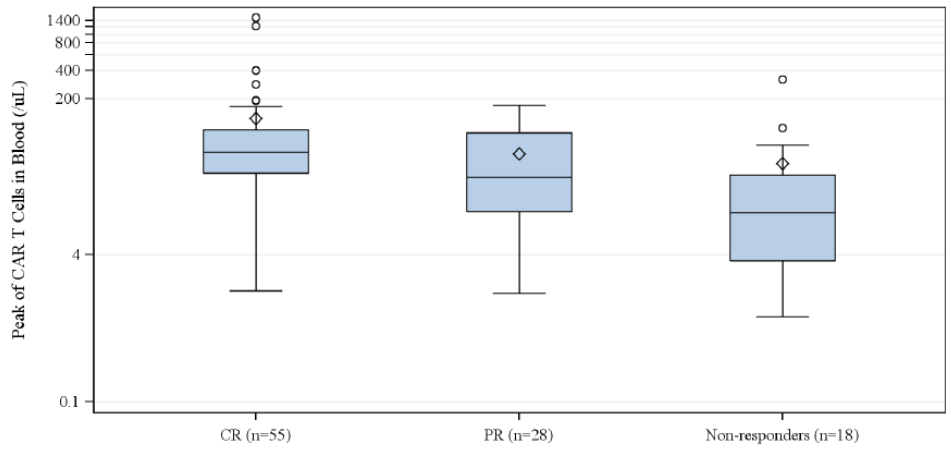
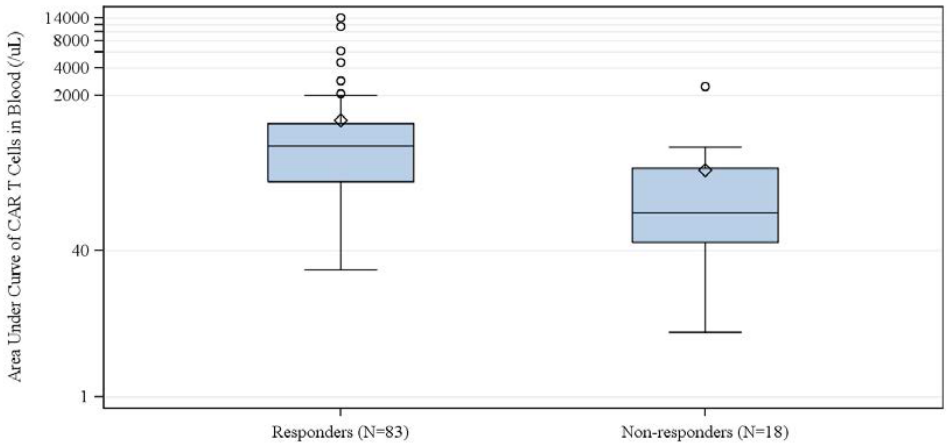


Figure 3: AUC for Number of Anti-CD19 CAR T Cells in Blood (/µL) by Responder Groups (mITT Analysis Set)



Special populations

Patients with HIV, HBV and HCV infection

There is no clinical experience with active HIV, HBV or HCV infection.

Paediatric population

The safety and efficacy of YESCARTA in children and adolescents below 18 years of age have not yet been established. No data are available.

Elderly

No dose adjustment is required in patients ≥ 65 years of age. Efficacy was consistent with the overall treated patient population.

Table 2: Older patients in clinical pharmacology studies

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
ZUMA-1	23/108	4/108	0/108
NCI-09-C-0082	2/13	0/13	0/13
TOTAL*	25/121	4/121	0/121

* Clinical Pharmacology is supported by 108 subjects treated in ZUMA-1 and 13 subjects treated in NCI-09-C-0082. The 108 subjects treated in ZUMA-1 are also included in the Table on AEs in older patients.

Age and gender

No difference could be observed for covariates such as age and gender in terms of PK parameters.

Race

There was a limited sample size of Asian patients (N=3). Both the CAR-T-cell peak and the AUC are much higher in asians compared to the group of whites (n=87) and others (n=11). However, it should be noted that the sample size for Asian subjects is very small.

The median CAR-T cell peak and the AUC of the white patients (n=87) were comparable with those of “others” (n=11), while the CAR-T cell peak of the asians was about 20 times and the AUC 10 times/ 16 times higher compared to both other groups. However, it should be noted that the sample size for non-white subjects is small.

Pharmacokinetic interaction studies

No PK drug interaction studies have been conducted (see discussion on clinical pharmacology).

In ZUMA-1 phase 2 (cohort 1+2), 27 subjects (27%) were treated with steroids, 43 subjects (43%) were treated with tocilizumab, 25 subjects (25%) were treated with steroids and tocilizumab, 17 subjects (17%) were treated with vasopressors, and 6 subjects (6%) were treated with immunoglobulins. In Zuma-1 the expansion of anti-CD19 CAR T-cells was not diminished in subjects who received tocilizumab or steroids compared with those who did not. The median peak level of anti-CD19 CAR-T cells was higher in subjects who received tocilizumab/steroids (61.1 and 49.7 cells/µL respectively) versus subjects who did not received tocilizumab/steroids (26.5 and 32.2 cells/µL respectively). Levels (peak and AUC at 1 month) of anti-CD19 CAR T-cells, objective response rate, and the PFS rate at 6 months were similar in subjects who received reactive tocilizumab and/or corticosteroids compared to those who did not.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

No specific mechanism of action studies have been conducted.

Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy that involves autologous or allogeneic T-cells engineered to express CARs directed against tumour-associated antigens.

KTE-C19 is a form of autologous CAR T-cell therapy directed against CD19, the surface antigen expressed in DLBCL and other aggressive B-cell lymphomas. The structure of the anti-CD19 CAR construct used for production and the product's mechanism of action are shown below.

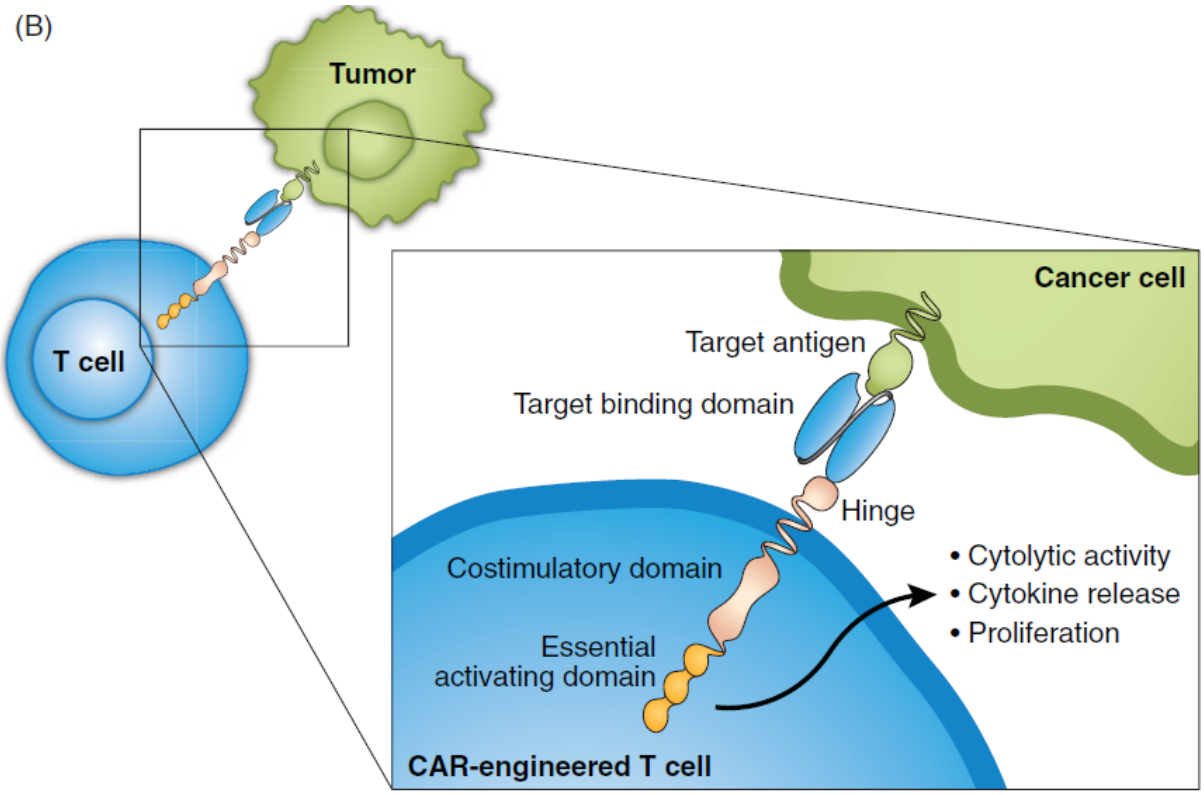


Figure 4: Anti-CD19 CAR T Cells / Yescarta: Vector Construct and Mode of Action (Roberts et al, 2017)
A preparation of autologous peripheral blood T-lymphocytes that have been transduced with a gamma retroviral vector expressing a CAR consisting of an anti-human CD19 single chain variable fragment (scFv) coupled to the costimulatory signalling domain CD28 and the zeta chain of the T-cell receptor (TCR)/CD3 complex (CD3 zeta), activates the downstream signalling cascades that lead to activation, proliferation, cytokine production and acquisition of effector functions, such as cytotoxicity.

Primary and secondary pharmacology

NCI 09-C-0082

Up to 44 biomarkers were evaluated in serum samples in NCI 09-C-0082. Levels of homeostatic, inflammatory/regulatory cytokines, chemokines, and immune effector molecules peaked sequentially within 7 days after treatment, in parallel with anti-CD19 CAR T-cell expansion, and generally resolved to near baseline levels within 2 to 3 weeks after infusion. The tumour samples have been analysed for CD19 expression in NCI study (per inclusion criteria).

Levels of homeostatic, inflammatory/regulatory cytokines, chemokines, and immune effector molecules peaked sequentially within 7 days after treatment, in parallel with anti-CD19 CAR T-cell expansion, and generally resolved to near baseline levels within 2 to 3 weeks after infusion. Nine of the 11 key analytes showed increases of more than 2-fold over baseline in ≥ 30% of subjects.

Table 3: Incidence of ≥ 2-fold Increases in Selected Serum Cytokines at Peak and Last Visit

Cytokine	≥ 2-fold Change from Baseline at Peak	≥2-fold Change from Baseline at Last Visit[1]
CRP (mg/L)	10/13 (76.9%)	2/13 (15.4%)
Granzyme B (pg/mL)	11/13 (84.6%)	2/13 (15.4%)
IFN-γ (pg/mL)	12/13 (92.3%)	1/13 (7.7%)
IL-6 (pg/mL)	11/13 (84.6%)	1/13 (7.7%)
IL-8 (pg/mL)	10/13 (76.9%)	3/13 (23.1%)
IL-10 (pg/mL)	12/13 (92.3%)	1/13 (7.7%)
IL-13 (pg/mL)	4/13 (30.8%)	0/13 (0.0%)
IL-15 (pg/mL)	13/13 (100.0%)	3/13 (23.1%)
TNF-α (pg/mL)	6/13 (46.2%)	0/13 (0.0%)

Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

ZUMA-1 phase 1 / 2

Forty-four (44) analytes (including cytokines, chemokines, and effector-related markers) were evaluated in serum samples at the following time points: prior to conditioning chemotherapy, prior to axicabtagene ciloleucel infusion, and at various time points after the infusion, up to Day 28. These analytes encompass a panel of homeostatic, inflammatory, and immune modulating cytokines, chemokines, and immune effector–related markers. Several cytokines were observed to increase after infusion of axicabtagene ciloleucel, peaking within 14 days of infusion and generally decreasing towards the baseline levels within 1 month. Notably, IL-15 was induced following conditioning chemotherapy, whereas all other cytokines were induced following the cell infusion. IFN-Gamma was not induced following conditioning chemotherapy, but showed a meaningful increase following the cell infusion from 7.5 pg/mL (7.5, 1876.0) to 477.4 (7.5, 8209.2). Analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of IL-15, as well as IL-6, were associated with Grade 3 or higher neurologic events and Grade 3 or higher CRS (please refer to clinical safety).

Table 4: Percentage of Subjects with ≥ 2-fold Increases in Analytes in ZUMA-1 Phase 2 (Safety Analysis Set)

Cytokine	At Peak (N = 90)	At Day 28 (N = 60)
	N (%)	N (%)
CRP (mg/L)	67 (74.4)	3 (5.0)
Granzyme B (pg/mL)	79 (87.8)	16 (26.7)
IFN-gamma (pg/mL)	87 (96.7)	22 (36.7)
IL-1 RA (pg/mL)	59 (65.6)	2 (3.3)
IL-2 R alpha (pg/mL)	64 (71.1)	14 (23.3)
IL-6 (pg/mL)	78 (86.7)	30 (50.0)
IL-8 (pg/mL)	73 (81.1)	3 (5.0)
IL-10 (pg/mL)	83 (92.2)	15 (25.0)
IL-12 P40 (pg/mL)	13 (14.4)	5 (8.3)
IL-12 P70 (pg/mL)	15 (16.7)	2 (3.3)
IL-13 (pg/mL)	6 (6.7)	0 (0.0)
IL-15 (pg/mL)	88 (97.8)	17 (28.3)
TNF alpha (pg/mL)	24 (26.7)	2 (3.3)

[1] The same percentage of subjects showed a ≥ 2-fold increase in IL-15 over baseline at Day 0.

Abbreviations: IFN, interferon; IL, interleukin; CRP, C-reactive protein; ra, receptor antagonist; Rα, receptor alpha; TNF, tumor necrosis factor.

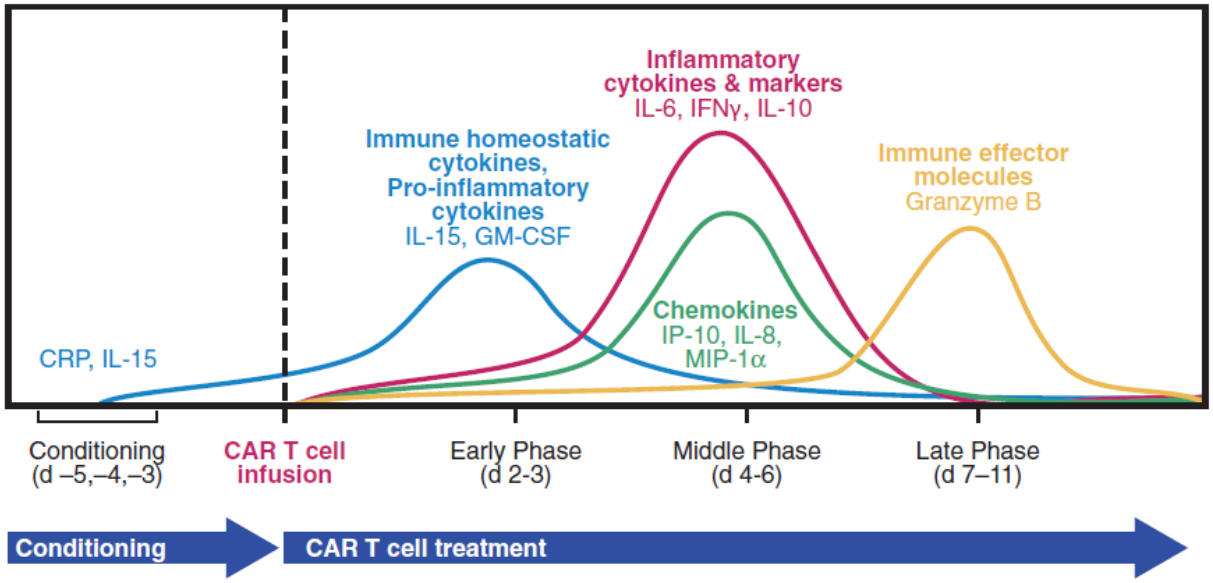


Figure 5 key cytokines and chemokines during CAR T cell therapy. CRP: C-reactive protein; d: day; GM-CSF: granulocyte- macrophage colony-stimulating factor; IFN: interferon; IL: interleukin; MIP: macrophage inflammatory protein (Roberts et al, 2017)

The tumour samples have been analysed for CD19 expression in ZUMA-1 study (retrospective analysis). In view of secondary pharmacology, B-cells were counted at baseline and 3, 6, 9, 12, and 15 months after the infusion of Yescarta to identify b-cell aplasia as on-target off-tumour toxicity. Undetectable B cells were defined by B-cell counts based on the lower limit of detection for the assay, with a cut-off of B cell count < 61 B cells/µL (Kochenderfer, 2012). B-cell aplasia was assessed among evaluable Phase 1 and Phase 2 subjects using a qualified flow cytometry assay on cryopreserved subject PBMCs. B-cell aplasia was defined as B cells < lower limit of quantitation (LLOQ, defined as CD19+, CD20+, or double positive for CD19+ and CD20+

events < 0.017 B cells as a percentage of viable leukocytes, with 10000 or more viable leukocyte events acquired in the assay. Baseline samples were taken prior to conditioning chemotherapy and axicabtagene ciloleucel infusion. At baseline (n = 80 subjects), 48 subjects (60%) had no detectable B cells, 28 subjects (35%) had detectable B cells, and 4 subjects (5%) were not determined due to a low event count. At Month 3 (n = 84 subjects), 65 subjects (77%) had no detectable B cells, 16 subjects (19%) had detectable B cells, and 3 subjects (4%) were not determined due to a low event count.

At Month 6 (n = 23 subjects), 19 subjects (83%) had no detectable B cells, and 4 subjects (17%) had detectable B cells. At Month 9 (n = 5 subjects), 5 subjects (100%) had no detectable B cells.

At Month 15 (n = 2), 2 subjects (100%) had no detectable B cells.

Additionally, 8 subjects (10%) in Cohort 1 and 11 subjects (11%) in Cohort 1 and 2 combined had experienced Grade 1 or 2 hypogammaglobulinaemia; 6 of these subjects received immunoglobulins as treatment for the hypogammaglobulinaemia during the hospitalization period. In addition, 1 subject received immunoglobulins for treatment of hypogammaglobulinaemia after the hospitalization period.

2.4.4. Discussion on clinical pharmacology

Results from the NCI 09-C-0082 and ZUMA-1 showed that peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after YESCARTA infusion. In the primary analysis of ZUMA-1 Phase 2, he median peak level of anti-CD19 CAR T cells in the blood (C_{max}) were 41.9 cells/µL (range: 0.8 - 1513.7 cells/µL), which decreased to a median of 2.1 cells/µL by 1 month (range 0 - 167.4 cells/µL) and to a median of 0.4 cells/µL by 3 months (range 0 - 15.8 cells/µL) after YESCARTA infusion .

The levels of anti-CD 19 declined by day 28 and declined to near background levels within 3 months.

The extent of T cell expansion does not appear to be related to the total dose of CAR-T cells with respect to one patient within NCI-09-C-0082 who received a higher dose (6 x 10^6 anti-CD19 CAR T-cells/kg instead of 2 x 10^6 anti-CD19 CAR-T cells/kg).

The number of anti-CD19 CAR T cells in blood was positively associated with objective response (CR or PR) based on the central assessment and the 12-month update. . The median anti-CD19 CAR T cell C_{max} levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/µL vs 21.2 cells/µL). Median $AUC_{Day\ 0\ -\ 28}$ in responding patients (n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days × cells/µL vs. 222.0 days × cells/µL).

Patients who had co-medication with steroids (n=26) and tocilizumab (n=43) showed increased Cmax and AUC-level. For the other covariates such as gender, age, race and tumour burden no significant impact on the pharmacokinetics became evident.

Several product characteristics of axicabtagene ciloleucel were studied in association with treatment outcomes: percent transduction, ex vivo IFN-γ production in a co-culture assay, as well as the percentage of product T-cell subsets (based on CCR7, CD45RA, CD4, and CD8 expression determined by flow cytometry; and total number of T cells or anti-CD19 CAR T cells infused). Given a limited sample size and exploratory nature of analyses, the results should be taken with caution, product characteristics did not appear to be predictive of efficacy outcomes. As to safety, interestingly the provided data suggests that products which

contain increased numbers of more differentiated T cells (Tcm, Tem and Teff) may be associated with higher probability of Grade 3 or higher CRS (See RMP).

In the NCI study, four of the five CRs had long-term durability with durations of remission of 56, 51, 44, and 38 months. CRs continued after recovery of non-malignant polyclonal B cells in three of four patients with long-term complete remissions without detectable levels of anti CD-19 CAR T-cells in the blood.

One subject in the study NCI 09-C0082 with ongoing CR who received a dose of 1 x 10^6 cells/kg had detectable anti-CD19 CAR-T cells at the last visit on Day 125 while other subjects with ongoing CRs had no detectable anti-CD19 CAR T- cells in the blood.

The results in regard to temporary relationship between persistence of CAR-T cells and B-cell aplasia have been provided for both NCI and ZUMA-1 studies. A decline in the number of subjects with detectable anti-CD19 CAR T cells was associated with an increase in the number of subjects with detectable B cells over time, indirectly indicating target engagement. Starting from month 9, about 20% of subjects do not have detectable CAR-T cells but experience B-cell recovery. In addition, an increase over time was observed in a subset of subjects who had undetectable anti-CD19 CAR T cells together with detectable B cells. Notably, a subset of subjects across all time points evaluated to date, had both detectable anti-CD19 CAR T cells and detectable B cells, albeit at very low levels. No data in regard to functional characteristics of persisting anti-CD19 CAR-T cells are available to date.

Demonstration of CD19 expression was not required for study eligibility, as the restricted expression of CD19 to both normal and most malignant B-cells to be well established by literature. The retrospective tissue analysis revealed that 92 % of enrolled patients were CD19 positive. Of note, 5/9 patients with a negative IHC-signal were responder. Reasons for potentially false-negative treatment results were degradation of CD19-antigen over time and a lower detection CD19-detection level in heterogenous tumours compared to homogenous, which are acknowledged. Overall, there was no overt relationship between the dose of anti-CD19 CAR+ T cells and their expansion and persistence in the peripheral blood. Likewise, to date, there was no apparent relationship between the anti-CD19 CAR+ T cell dose, the anti-CD19 CAR+ T cell persistence in the blood, and the clinical response or the toxicities related to this therapy, respectively.

The prophylactic use of systemic steroids is not recommended as it may interfere with the activity of Yescarta (see section 4.2. of the SmPC).

The pharmacodynamics of ZUMA-1 phase 2 may support the median time to peak level of anti-CAR-T-cells in blood after drug infusion. However, the comparative analysis between responder vs. non-responder showed, that biomarker such as IFN-Gamma or IL-15 were not positively correlated with the treatment outcome, neither for the depth nor for the duration of response. There is currently no evidence of a positive correlation between certain biomarkers such as IFN-Gamma and IL-15 and a positive treatment outcome (See discussion on clinical efficacy and RMP).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic and pharmacodynamic assessments were based on the known mechanism of action of anti-CD19 CAR T cell and the current knowledge of the safety profile of the conditioning chemotherapy and anti-CD19 CAR T-cell infusion.

Clinical pharmacology data with Yescarta are considered sufficient to support the MAA.

The CHMP endorsed the CAT assessment regarding the conclusions on the Clinical pharmacology as described

above.

Clinical efficacy

Introduction

The Applicant has submitted one key phase II study (ZUMA-1 phase 2), one retrospective global patient-level pooled study (Scholar-1), supportive phase I study (Zuma-1 phase 1), and study NCI-09-C-0082. Since the efficacy results of ZUMA-1 phase 2 are to be compared with the results of Scholar-1, both studies are considered as main studies and studies ZUMA-1 phase 1 and NCI-09-C-0082 as supportive.

The current submission does not include subjects enrolled in Phase 2 Cohort 3 because enrollment into Cohort 3 was initiated in September 2016 and results from this cohort will be described separately.

2.4.6. Dose response studies

NCI 09-C-0082:

Dosing of the conditioning chemotherapy agents and Yescarta was based on the results NCI study 09-C-0082, a Phase 1 open label study of the safety and feasibility of anti-CD 19 CAR T-cells in subjects with advanced B-cell malignancies.

Because previous studies have shown an association between adequate lymphodepletion and adoptively transferred T−cell expansion and function in animal models, lymphodepletion was included for all subjects. The NCI protocol underwent numerous amendments that altered the doses of conditioning chemotherapy agents, post infusion IL-2, and anti-CD19 CAR T-cells.

A total of 14 cohorts were enrolled. Cohorts 1 through 10 used fresh cells. Cohorts 1 through 9 used high doses of cyclophosphamide (60 mg/kg or 30 mg/kg for 2 days) and fludarabine (25 mg/m2 for 5 days) as conditioning chemotherapy and high doses of anti-CD19 CAR T-cells (3.0×10^6 cells/kg to 3.0×10^7 cells/kg).

Cohorts 11-14 used cryopreserved cells. Cohorts 11 and 12 were planned to use the same conditioning chemotherapy as Cohort 10; the target anti-CD19 CAR T-cell doses were increased to 2×10^6 cells/kg and 6×10^6 cells/kg, respectively, to assess the potential need for higher doses of the cryopreserved cell product. Cohorts 13 and 14 explored a cyclophosphamide dose of 500 mg/m2 for 3 days, with the same doses of fludarabine and anti-CD19 CAR T-cell as used in Cohort 11. The subjects enrolled in Cohorts 11, 12, 13, and 14 represent a group similar to study ZUMA-1 with respect to disease status and treatment.

ZUMA-1 phase 1

Based on the response and safety observations described above for the NCI study and the need to achieve adequate lymphodepletion and therapeutic levels of anti-CD19 CAR T-cells without intolerable toxicity, the ZUMA-1 study used a regimen of cyclophosphamide 500 mg/m2 dose and fludarabine 30 mg/m2 given concurrently for 3 days and a target Yescarta dose of 2×10^6 anti-CD19 CAR T cells/kg. For subjects weighing > 100 kg, the Yescarta dose was fixed to 2×10^8 cells.

The Phase 1 of ZUMA-1 planned for alternatively reducing conditioning chemotherapy regimens and Yescarta doses if the initial dosing was not well tolerated. The DLT definition in the KTE-C19-101 study was applied to the NCI study (09-C-0082; IND 13871) data in group 3.

Seven subjects were treated in Phase 1. Six subjects were evaluable for toxicity per protocol, and 1 of the 6 subjects experienced dose-limiting toxicities (Grade 4 encephalopathy on Day 1 and Grade 4 CRS on Day 6, comprising acute kidney injury, left ventricular failure, metabolic acidosis, and hypotension). On Day 16, the subject developed Grade 5 AE of intracranial haemorrhage.

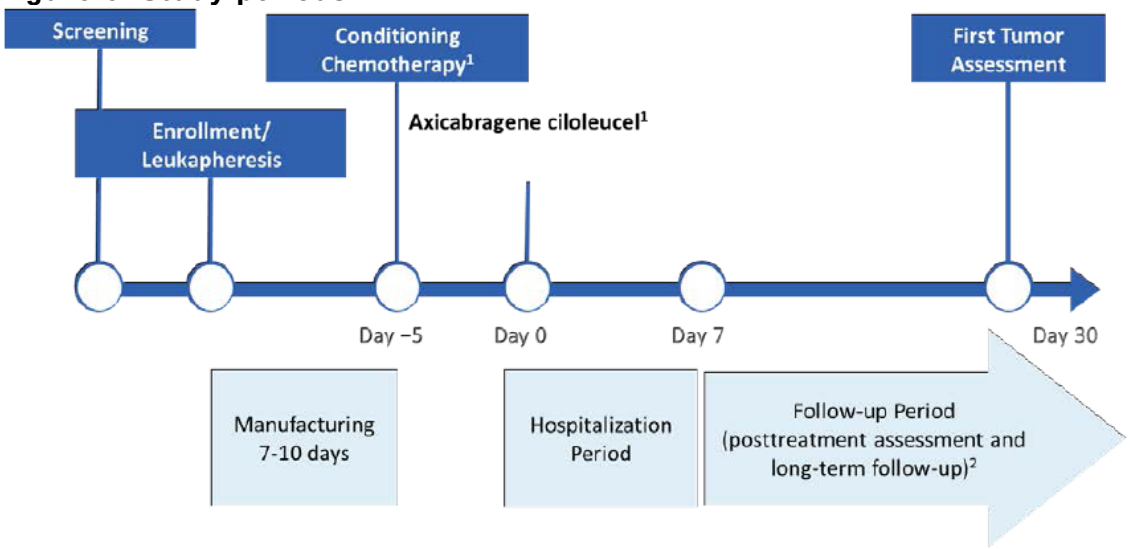
Additional safety precautions were adopted in the protocol following these events. The safety review team considered the Phase 1 regimen to be tolerable; therefore, the same doses of cyclophosphamide, fludarabine, and anti-CD19 CAR T-cells were employed in Phase 2.

2.4.7. Main study: ZUMA-1 phase 2 :

Methods

This was a single-arm, multicenter study and evaluated the use of a single infusion of axicabtagene ciloleucel in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NHL), which includes those patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL). All patients had histologically confirmed aggressive B-cell NHL based on the WHO-classification of 2008.

Figure 6. Study periods



1 Conditioning chemotherapy of 500 mg/m2 cyclophosphamide and 30 mg/m2 fludarabine on Day −5, Day − 4, Day −3 is followed by a target of 2 × 10^6 (± 20%) CAR T cells/kg (minimum 1×10^6 CAR T cells/kg) on Day 0.

2 Long-term follow-up for disease status and survival continued every 3 months through Month 18, then every 6 months through 5 years, and then annually for a maximum of 15 years.

Study Participants

Main inclusion criteria:

Efficacy-related inclusion criteria

1 Histologically confirmed aggressive B cell NHL, including the following types defined by WHO 2008:

- DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; OR

- primary mediastinal (thymic) large B cell lymphoma

- transformation of follicular lymphoma to DLBCL will also be included

2 Chemotherapy-refractory disease, defined as one or more of the following:

- No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy are excluded

- PD as best response to first-line therapy

- SD as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy

OR

-No response to second or greater lines of therapy

- PD as best response to most recent therapy regimen

- SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy

OR

- Refractory post-ASCT

-Disease progression or relapsed ≤12 months of ASCT (must have biopsy proven recurrence in relapsed subjects)

-if salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

3. Subjects must have received adequate prior therapy including at a minimum:

- anti-CD20 monoclonal antibody unless investigator determines that tumour is CD20 negative, and

- an anthracycline containing chemotherapy regimen;

- for subjects with transformed FL must have received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL

4. At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

5. Additional criteria specific for Cohort 3:

- Relapsed transplant ineligible DLBCL, PMBCL, or TFL (must have biopsy proven recurrence in relapsed subjects)

General criteria and safety-related inclusion criteria

6. MRI of the brain showing no evidence of CNS lymphoma

7. At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune

checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).

8. Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)

9. Age 18 or older

10. Eastern cooperative oncology group (ECOG) performance status of 0 or 1

11. ANC ≥1000/uL

12. Platelet count ≥75,000/uL

13. Absolute lymphocyte count ≥100/uL

14. Adequate renal, hepatic, pulmonary and cardiac function defined as:

o Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min

o Serum ALT/AST ≤2.5 ULN

o Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.

o Cardiac ejection fraction ≥ 50% ,no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings

o No clinically significant pleural effusion

o Baseline oxygen saturation >92% on room air

15. Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

Main exclusion criteria:

- History of malignancy other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years; History of Richter's transformation of CLL
- Autologous stem cell transplant within 6 weeks of planned KTE-C19 infusion; History of allogeneic stem cell transplantation
- Prior CD19 targeted therapy with the exception of subjects who received KTE-C19 in this study and are eligible for re-treatment; Prior chimeric antigen receptor therapy or other genetically modified T cell therapy
- History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
- Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite Medical Monitor.
- Known history of infection with HIV or hepatitis B (HBsAg positive) or hepatitis C virus (anti- HCV positive). A history of hepatitis B or hepatitis C was permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.
- Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted
- Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases

- History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
- Subjects with cardiac atrial or cardiac ventricular lymphoma involvement; History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrolment
- Requirement for urgent therapy due to tumour mass effects such as bowel obstruction or blood vessel compression
- Primary immunodeficiency
- History of deep vein thrombosis or pulmonary embolism within 6 months of enrollment
- Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
- History of severe immediate hypersensitivity reaction to any of the agents used in this study
- Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen
- Women of child-bearing potential who are pregnant or breastfeeding; Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-C19
- In the investigators judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation
- History of autoimmune disease (e.g. Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

Criteria for retreatment

Subjects who achieve a PR or CR will have an option to receive a second course of conditioning chemotherapy and KTE-C19 under the following conditions:

- Subject had a PR or CR at the Month 3 disease assessment

- Subjects disease subsequently progressed greater than 3 months after KTE-C19 infusion

- CD19 tumour expression confirmed locally by biopsy after disease progression and prior to retreatment

- Subject continues to meet the original study eligibility criteria with exception of prior KTE-C19 use in this study

- Subject has not received subsequent therapy for the treatment of lymphoma

- Subject did not experience a DLT in phase 1 or a comparable toxicity in phase 2

- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ grade 1 or returned to baseline prior to re-treatment

-Subject does not have known neutralizing antibodies (exception: if a non-neutralizing HAMA or HABA antibody develops subject may be retreated if they meet the original study eligibility criteria)

A maximum of 1 retreatment course could occur per subject.

Treatments

Screening and Enrolment

In addition to meeting the eligibility criteria, subjects must have had no evidence of a clinically significant infection prior to leukapheresis. For Phase 1, enrollment was defined as anyone who signed consent and met

the eligibility criteria prior to the leukapheresis. For Phase 2, after a subject commenced leukapheresis, the subject was considered enrolled into the study.

Leukapheresis and Cell processing

Investigative sites were instructed to perform leukapheresis per local requirements and follow the instrument operator's manual. A minimum of were to be processed with a goal of obtaining approximately. The bag containing leukapheresed cells was to be placed into a shipping container for transport at 1°C to 10°C to the manufacturing facility. Upon receipt, each subject's respective leukapheresed product was. T cells in the PBMC fraction were then activated. The monocytes in the PBMC preparation present the to T cells, resulting in crosslinking of the T-cell receptor complex and downstream signaling. This activation process renders the T cells permissive for transduction. This population of stimulated T cells was then transduced with a retroviral vector that is manufactured in a GMP process to introduce the CAR gene (Lu et al, 2016).

Chemotherapy

Subjects were to receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of KTE-C19 in vivo.

Objectives

Primary Objective for Zuma Phase II was to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with DLBCL, PMBCL, and TFL.

Secondary Objective for cohorts 1 and 2 were to assess safety and tolerability of KTE-C19 and additional efficacy endpoints.

Secondary Objective specific to cohort 3 was to assess the impact of a prophylactic regimen on the rate of CRS and neurotoxicity and to assess the change in EQ-5D scores from baseline to Month 6.

Outcomes/endpoints

Primary Endpoint:

Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT).

Phase 2: Objective response rate (ORR), defined as a CR or PR per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by study investigators. All subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered non-responders.

Secondary Endpoints (for Phase 2):

- ORR according to the central review, based on the IWG 2007 criteria (Cheson et al, 2007), defined as the proportion of subjects with either a CR or PR while on study. The best overall response for each subject was based on the assessments of response (CR, PR, SD, PD, not evaluable [NE], and not done [ND]).
- Duration of Response (DOR) according to the investigator's assessment, and by central review, both based on IWG 2007 criteria (Cheson et al, 2007), defined as the time from the first objective response to disease progression or death due to disease relapse or drug-related toxicity.

- Progression Free Survival (PFS) according to the investigator's assessment, and by central review, both based on IWG 2007 criteria (Cheson et al, 2007), defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause.
- Overall Survival (OS) defined as the time from the axicabtagene ciloleucel infusion to the date of death from any cause.
- Safety: Incidence of AEs, significant laboratory abnormalities, and presence of RCR or antibodies to FMC63 or bovine serum albumin in subjects' blood.

Subjects had their first post KTE-C19 infusion planned PET-CT tumour assessment 4 weeks following the KTE-C19 infusion, every 3 months during the post treatment until 24 moths, with no further imaging in long term follow-up portion of the study. In addition to the investigators assessment, PET-CT scans of all subjects evaluated for disease response for phase 2 had to be submitted to and reviewed by an independent central reviewer. For subjects who discontinued the study due to an assessment of progressive disease which was not subsequently confirmed by a central radiology reviewer, any additional imaging data, subsequent to the image in question will be submitted to the central reviewer to confirm disease response.

A bone marrow aspirate and biopsy had to be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007), a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment.

Response assessment requirements were per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007).

Sample size

For Phase 1, a 6 + 3 design was used which has at least 50% probability to detect AEs with 33% incidence or greater and was deemed to have an adequately high probability of stopping in the presence of DLT while minimizing subjects exposed. Approximately 6-24 subjects with DLBCL, PMBCL or TFL were planned to be enrolled to evaluate the safety of KTE-C19 regimens.

Planned enrolment was approximately 72 subjects for Phase 2 Cohort 1 (DLBCL) and at least 20 subjects for Phase 2 Cohort 2 (PMBCL and TFL). The single-arm design was planned to test for an improvement in ORR in Cohort 1 and in Cohorts 1 and 2 combined relative to a historical control rate. Given the sample size and taking multiplicity into account (see *Statistical Methods*), Phase 2 Cohorts 1 and 2 had at least 90% power with a 1-sided alpha of 0.025 to distinguish between an active therapy with a true response rate of 40% when compared with a therapy with a response rate of 20% or less.

Randomisation

Not applicable. This is a single-arm study.

Blinding (masking)

Not applicable. The study was an open-label study.

Statistical methods

The statistical hypothesis was that the ORR for subjects treated with axicabtagene ciloleucel in cohorts 1 and 2 is significantly greater than 20%.

No hypothesis will be tested in cohort 3. Cohort 3 is designed to estimate the response rate in relapsed / refractory transplant ineligible DLBCL, PMBCL, or TFL.

Analysis sets

The protocol specified 2 analysis sets for phase I (safety phase), a DLT evaluable set (patients who received the target and were followed for at least 30 days *or* patients who received a dose of anti-CD19 CAR+ T cells lower than the target for that cohort and experienced a DLT during the 30 day post-infusion period), and a safety set (all subjects treated with any dose of KTE-C19). For ORR, a mITT set as defined for phase II will be used.

For phase II, the protocol specified 3 analysis sets, i.e.

- a modified intent to treat set (mITT) consisting of all subjects *enrolled and treated* with KTE-C19 at a dose of at least 1 x 10^6 anti-CD19 CAR+ T cells/kg
- a safety set consisting of all subjects treated with any dose of KTE-C19
- the full analysis set (FAS) consisting of all enrolled (all leukapheresed) subjects (otherwise described as ITT).

The primary analysis of efficacy used the mITT set. The FAS was used for sensitivity analyses.

Methods

For the primary endpoint the objective response rate with exact 2-sided 95% confidence intervals was to be computed. For cohorts 1 and cohorts 1 and 2 combined, an exact binomial test was to be used to compare the observed response rates to a response rate of 20%.

For the duration of response, a competing-risk analysis method (Pepe 1991, Fine and Gray 1999) was to be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence of non-disease related mortality (the competing risk) will be estimated along with 2-sided 95% confidence intervals at 3-month intervals. Kaplan-Meier estimates and 2-sided 95% confidence intervals were to be used for PFS and OS. Landmark analyses at 3 months intervals were to be provided for survival endpoints.

Multiplicity and timing of analyses

Alpha splitting according to Song and Chi (2007) and Wang et al (2007) was defined in order to control the overall type 1 error at 0.025 (one-sided) for testing of cohort 1 and the combined cohorts 1+2. Consequently, a significance level of 0.022 was used for cohort 1, and 0.0075 for cohorts 1+2. In order to control the type 1 error maximum patient numbers per cohort were conservatively assumed. In cohort 1, two interim analyses were planned. One interim analysis for futility was planned after 20 subjects with 3 months follow-up data in the mITT set. A second interim analysis for efficacy was planned after 50 subjects with 3 months follow-up in the mITT set. The final analysis was planned after 72 subjects with 6 months follow-up. A Pocock boundary of the of the Lan-DeMets family of alpha spending functions was pre-specified for the efficacy interim analysis leading to a nominal significance level of 0.017 in the second interim analysis and 0.011 in the final analysis.

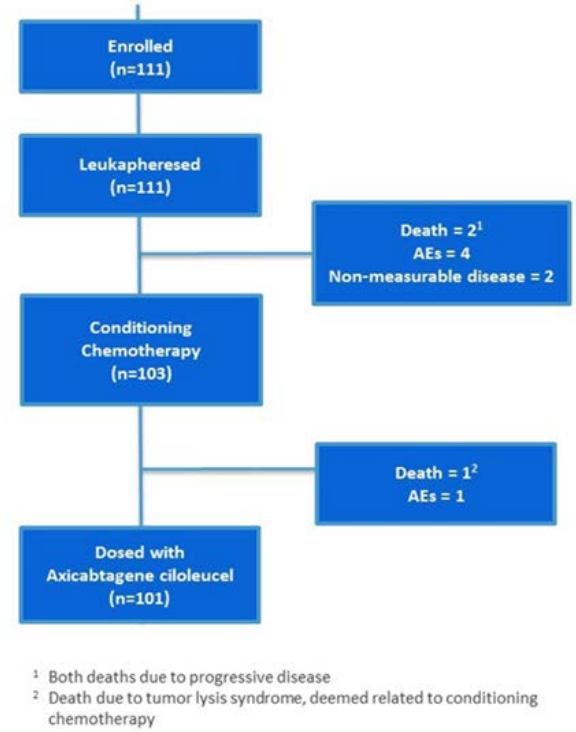
The primary analysis of cohorts 1 and 2 combined was planned to be performed when additional 20 subjects in the mITT set of cohort 2 have had the opportunity to be evaluated for response at 6 months after the target KTE-C19 infusion.

Results

ZUMA-1

Participant flow

Figure 7: Participant flow in ZUMA-1



[1] Both deaths due to progressive disease
[2] Death due to tumor lysis syndrome, deemed related to conditioning chemotherapy

Recruitment

ZUMA-1 phase 2 was conducted at 24 sites (23 in the US and 1 in Israel). While the data cut-off for primary analysis was 27th January 2017 with follow up-data through 11 Aug 2017, a long-term follow up of 15 years for those patients in response was foreseen.

Of 111 enrolled and leukapherized patients, 101 received the IMP: 77 patients with DLBCL in cohort 1 and 24 patients with either TFL or PMBCL in cohort 2. Of the 10 patients who failed to receive the product, one was due to manufacturing failure. The further 9 patients were not treated due to progressive disease, serious adverse reactions following leukapharesis or chemotherapy or due to undetectable disease.

The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days) and the median time from leukapheresis to infusion was 23 days (range: 15 to 72 days). The median dose was 2.0x 10^6 CAR-positive T cells/kg (range 1.1 to 2.2 x10^6 cells/kg).

Conduct of the study

The study protocol was amended 5 times and a total of 19 deviations were reported for 17 subjects (17%; 14 subjects in Cohort 1 and 3 subjects in Cohort 2). The most frequently occurring relevant protocol deviation (11 subjects) was baseline positron emission tomography–computed tomography (PET-CT) not performed within 28 days of conditioning chemotherapy. In these patients, the baseline scan was done between day -29 and -41 days relative to conditioning chemotherapy. None of these patients received anti-cancer therapy during the interval. Steroid infusion within 5 days prior to treatment with Yescarta, which applied for one of the 11 patients, is not considered to bias the efficacy data.

Baseline data

Table 5. Demographics (Safety Analysis Set):

		Phase 2		
	Phase 1 (N = 7)	Cohort 1 (N = 77)	Cohort 2 (N = 24)	Total (N = 101)
Age (years)				
n	7	77	24	101
Mean (Std Dev)	52.4 (17.5)	57.4 (10.6)	53.0 (15.5)	56.3 (12.0)
Median	59.0	58.0	57.0	58.0
Min, Max	29, 69	25, 76	23, 76	23, 76
Age Category n(%)				
<65 Years	4 (57)	60 (78)	17 (71)	77 (76)
>=65 Years	3 (43)	17 (22)	7 (29)	24 (24)
Sex n(%)				
Male	5 (71)	50 (65)	18 (75)	68 (67)
Female	2 (29)	27 (35)	6 (25)	33 (33)
Ethnicity n(%)				
Hispanic or Latino	1 (14)	16 (21)	2 (8)	18 (18)
Not Hispanic or Latino	6 (86)	61 (79)	22 (92)	83 (82)
Race n(%)				
Asian	0 (0)	1 (1)	3 (13)	4 (4)
Black or African American	1 (14)	3 (4)	1 (4)	4 (4)
White	6 (86)	71 (92)	19 (79)	90 (89)
Others	0 (0)	2 (3)	1 (4)	3 (3)
Country n(%)				
United States	7 (100)	77 (100)	23 (96)	100 (99)
Israel	0 (0)	0 (0)	1 (4)	1 (1)

Table 6. Baseline Characteristics (Safety Analysis Set)

		Phase 2		
	Phase 1 (N = 7)	Cohort 1 (N = 77)	Cohort 2 (N = 24)	Total (N = 101)
ECOG Performance Status n(%)				
0	4 (57)	28 (36)	14 (58)	42 (42)
1	3 (43)	49 (64)	10 (42)	59 (58)
Disease Type n(%) Local				
DLBCL	7 (100)	77 (100)	0 (0)	77 (76)
PMBCL	0 (0)	0 (0)	8 (33)	8 (8)
TFL	0 (0)	0 (0)	16 (67)	16 (16)
Disease Subtype n(%)				
DLBCL not otherwise specified	7 (100)	75 (97)	0 (0)	75 (74)
DLBCL associated with chronic inflammation	0 (0)	1 (1)	0 (0)	1 (1)
Primary mediastinal (thymic) large B cell lymphoma	0 (0)	0 (0)	8 (33)	8 (8)
Transformation of follicular lymphoma to DLBCL	0 (0)	0 (0)	16 (67)	16 (16)
Other	0 (0)	1 (1)	0 (0)	1 (1)
Disease Type Central Read n(%)				
DLBCL	6 (86)	63 (82)	6 (25)	69 (68)
PMBCL	0 (0)	0 (0)	4 (17)	4 (4)
TFL	0 (0)	0 (0)	9 (38)	9 (9)
Other	1 (14)	1 (1)	1 (4)	2 (2)
CD19 Positivity n(%)				
Yes	3 (43)	56 (73)	18 (75)	74 (73)
No	2 (29)	7 (9)	1 (4)	8 (8)
CD19 H-score				
n	5	63	19	82
Mean (Std Dev)	166.0 (151.9)	184.6 (103.9)	196.6 (99.4)	187.4 (102.4)
Median	260.0	210.0	250.0	210.0
Min, Max	0, 290	0, 300	0, 300	0, 300
Disease Stage n(%)				
I	2 (29)	2 (3)	2 (8)	4 (4)
II	1 (14)	8 (10)	3 (13)	11 (11)
III	2 (29)	20 (26)	8 (33)	28 (28)
IV	2 (29)	47 (61)	11 (46)	58 (57)
Presence of B Symptoms n(%)				
Yes	1 (14)	7 (9)	2 (8)	9 (9)
No	6 (86)	70 (91)	22 (92)	92 (91)
S (Splenic Involvement) n(%)				
Yes	1 (14)	16 (21)	0 (0)	16 (16)
No	6 (86)	61 (79)	24 (100)	85 (84)
E (Extranodal Disease) n(%)				

	Phase 1 (N = 7)	Phase 2 Cohort 1 (N = 77)	Phase 2 Cohort 2 (N = 24)	Total (N = 101)
Yes	3 (43)	54 (70)	16 (67)	70 (69)
No	4 (57)	23 (30)	8 (33)	31 (31)
X (Bulky Disease) n(%)				
Yes	0 (0)	14 (18)	3 (13)	17 (17)
No	7 (100)	63 (82)	21 (88)	84 (83)
Bone Marrow assessment at Baseline n(%)				
Negative	6 (86)	65 (84)	18 (75)	83 (82)
Positive	1 (14)	8 (10)	3 (13)	11 (11)
Not Assessed	0 (0)	4 (5)	3 (13)	7 (7)
International Prognostics Index (IPI) n(%)				
0	1 (14)	3 (4)	1 (4)	4 (4)
1	2 (29)	13 (17)	10 (42)	23 (23)
2	2 (29)	24 (31)	2 (8)	26 (26)
3	1 (14)	23 (30)	7 (29)	30 (30)
4	1 (14)	14 (18)	4 (17)	18 (18)
Refractory Subgroup n(%)				
Primary refractory	0 (0)	2 (3)	0 (0)	2 (2)
Refractory to 2nd or greater line therapy	3 (43)	59 (77)	19 (79)	78 (77)
Relapse post ASCT	4 (57)	16 (21)	5 (21)	21 (21)
Prior Autologous Stem Cell Transplant (ASCT) n(%)				
Yes	4 (57)	18 (23)	7 (29)	25 (25)
No	3 (43)	59 (77)	17 (71)	76 (75)
Number of Prior Chemotherapy Regimen n(%)				
1	0 (0)	2 (3)	0 (0)	2 (2)
2	1 (14)	26 (34)	3 (13)	29 (29)
3	5 (71)	22 (29)	8 (33)	30 (30)
4	1 (14)	20 (26)	8 (33)	28 (28)
5	0 (0)	4 (5)	2 (8)	6 (6)
>5	0 (0)	3 (4)	3 (13)	6 (6)
Prior Anti-CD20 mAb n(%)				
Yes	7 (100)	77 (100)	24 (100)	101 (100)
Prior Anthracycline n(%)				
Yes	7 (100)	77 (100)	24 (100)	101 (100)
Prior Platinum n(%)				
Yes	6 (86)	68 (88)	21 (88)	89 (88)
No	1 (14)	9 (12)	3 (13)	12 (12)
Response to last Chemotherapy Regimen (for those not relapsed post ASCT) n(%)				
Stable Disease	0 (0)	10 (13)	4 (17)	14 (14)
Progressive Disease	3 (43)	51 (66)	15 (63)	66 (65)

	Phase 1 (N = 7)	Phase 2 Cohort 1 (N = 77)	Phase 2 Cohort 2 (N = 24)	Total (N = 101)
Tumor Burden (SPD) (mm2) (1)				
n	7	77	24	101
Mean (Std Dev)	2703.7 (2291.8)	4937.4 (4050.1)	5354.8 (5347.9)	5036.6 (4367.7)
Median	2457.0	3897.0	3173.5	3723.0
Min, Max	320, 6062	171, 19201	732, 23297	171, 23297

Abbreviations: ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma; Std Dev, standard deviation; SPD, sum of the product of the diameters.

A comparison of basic patient demographics in all leukapheresed (ITT) vs all treated (mITT) patients is given.

Table 7. Comparison of demographics for ZUMA-1 phase 2 (12 month analysis): ITT vs mITT

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**	**All treated (mITT) Cohort 1 + 2 (N = 101)**
Age (years)		
Median (min, max)	58 (23, 76)	58 (23, 76)
≥ 65	23%	24%
Male gender	69%	67%
Race		
White	85%	86%
Asian	4%	3%
Black	4%	4%
ECOG status		
ECOG 0	41%	42%
ECOG 1	59%	58%
Median number of prior therapies (min, max)	3 (1, 10)	3 (1, 10)
Patients with refractory disease to ≥ 2 prior lines of therapy	77%	76%
Patients relapsed within 1 year of ASCT	20%	21%
Patients with International Prognostic Index 3/4	46%	46%
Patients with disease stage III/IV	85%	85%

Numbers analysed

Table 8: ZUMA-1 Primary Analyses Population Data Set

		Phase 2		
	Phase 1 (N = 8)	Cohort 1 (N = 81)	Cohort 2 (N = 30)	Total (N = 111)
Subjects Screened n	11			124
Screen Failures n	3			13
Full Analysis Set (1) n(%)	8 (100)	81 (100)	30 (100)	111 (100)
All Leukapheresed Analysis Set (ALS) (2) n(%)	8 (100)	81 (100)	30 (100)	111 (100)
Subjects Treated with Conditioning Chemotherapy n(%)	7 (88)	77 (95)	26 (87)	103 (93)
Safety Analysis Set (3) n(%)	7 (88)	77 (95)	24 (80)	101 (91)
DLT Evaluable Set (4) Cohort A1 n(%)	6 (75)	NA	NA	NA
Safety Re-treatment Analysis Set n(%)	1 (13)	8 (10)	1 (3)	9 (8)

Modified Intent-to-Treat (mITT) (5) n(%)	NA	77 (95)	24 (80)	101 (91)
mITT Re-treatment Analysis Set n(%)	NA	8 (10)	1 (3)	9 (8)

Outcomes and estimation

The primary endpoint (superiority of ORR compared to a historic control ORR of 20%) was met in Phase 2 for Cohort 1 at the second interim analysis and subsequently in Cohorts 1 and 2 combined: In the interim analysis 51 patients with 3 months minimum follow-up were assessed. The ORR among these patients was 76 % (95% CI: 63%, 87%), p <0.0001. In the inferential analysis for the combined cohorts in 92 subjects who were followed for 6 months, the ORR was 82% (95% CI: 72%, 89%), P < 0.0001, with 52% CR rate and 29% PR rate.

Additionally, ORR among all 101 subjects treated in Phase 2 was 83% (95% CI: 74%, 90%), with a CR rate of 58%. The ORR among all 101 subjects based on central review was 72% (95% CI: 62%, 81%), with a CR rate of 51%, respectively. ORR in all 111 enrolled patients in Cohorts 1 and 2 was 77% (95% CI: 69%, 85%) with a CR rate of 55% per local investigator and 66% (95% CI: 56%, 75%) with a CR rate 47% per central reviewer (see Table below).

Table 9. Responses to Axicabtagene Ciloleucel in ZUMA-1 phase 2, cohorts 1 and 2, per central assessment in the Full Analysis Set (FAS)

	Cohort 1 (N = 81)	Cohort 2 (N = 30)	Phase 2 Overall (N = 111)
Number of Objective Responders (CR + PR) n (%)	52 (64)	21 (70)	73 (66)
95% Confidence Interval (Clopper-Pearson method)	53, 75	51, 85	56, 75
95% Confidence Interval (Wilson's method)	53, 74	52, 83	57, 74
95% Confidence Interval (Agresti-Coull method)	53, 74	52, 83	57, 74
95% Confidence Interval (Modified Jeffrey's method)	53, 74	52, 84	57, 74
P-value of Exact Test of ORR =< 20%	<.0001		<.0001
Complete Response (CR) n (%)	37 (46)	15 (50)	52 (47)
Partial Response (PR) n (%)	15 (19)	6 (20)	21 (19)
Stable Disease n (%)	17 (21)	1 (3)	18 (16)
Progressive Disease n (%)	6 (7)	1 (3)	7 (6)
Not Done (ND) n (%)	6 (7)	7 (23)	13 (12)

The median DOR based on the central review was 14.0 months (95% CI: 8.3, NE) in the mITT set. An ongoing response at the data-cut-off was observed for 38 subjects. Three subjects in Cohorts 1 and 2 combined underwent allogeneic SCT while in a response after treatment with axicabtagene ciloleucel; these subjects were not censored in the main analysis, but were censored in a sensitivity analysis. The median DOR in subjects who achieved a CR was not reached, the median follow-up time was 11.3 months.

Table 10. Sensitivity Analysis of Best Overall Response: Investigator Assessment per Cheson 2007 in all leukapherized Subjects (Full Analysis Set)

	Cohort 1 (N = 81)	Cohort 2 (N = 30)	Phase 2 Overall (N = 111)
Number of Objective Responders (CR + PR) n(%)	63 (78)	22 (73)	85 (77)
95% Confidence Interval (Clopper-Pearson method)	67, 86	54, 88	68, 84
95% Confidence Interval (Wilson's method)	68, 85	56, 86	68, 83
95% Confidence Interval (Agresti-Coull method)	68, 86	55, 86	68, 84
95% Confidence Interval (Modified Jeffrey's method)	68, 86	56, 87	68, 84
Complete Response (CR) n(%)	38 (47)	19 (63)	57 (51)
95% Confidence Interval (Clopper-Pearson method)	36, 58	44, 80	42, 61
Partial Response (PR) n(%)	25 (31)	3 (10)	28 (25)
95% Confidence Interval (Clopper-Pearson method)	21, 42	2, 27	17, 34

Table 11. Duration of Response Using Central Review per Cheson 2007 (mITT Analysis Set)

	Cohort 1 (N = 52)	Cohort 2 (N = 21)	Phase 2 Overall (N = 73)
Duration of Response			
No. of subjects	52	21	73
Censored (%)	26 (50)	15 (71)	41 (56)
KM Median (95% CI) DOR time (in month)	10.9 (5.4, NE)	NE (11.1, NE)	14.0 (8.3, NE)
Type of Events			
Disease Progression	22	5	27
Disease/treatment related Death	4	1	5
Censoring reason			
Response ongoing	25	13	38
Started new anti-cancer therapy	1	2	3
KM Estimate (95% CI) at			
3 Month	75.0 (60.8, 84.6)	89.5 (64.1, 97.3)	78.8 (67.4, 86.7)
6 Month	62.7 (47.8, 74.4)	84.2 (58.7, 94.6)	68.5 (56.2, 78.0)
9 Month	55.8 (40.8, 68.4)	78.9 (53.2, 91.5)	62.2 (49.5, 72.5)
12 Month	47.2 (31.8, 61.1)	62.0 (31.8, 81.9)	51.2 (37.5, 63.3)
Median Follow-up Time (in months) for DOR (reverse KM approach)	11.1 (10.6, 14.0)	11.3 (10.9, 14.1)	11.3 (10.9, 13.6)

Table 12. Summary of efficacy results for ZUMA-1 phase 2 (12 month analysis, independent review committee)

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**	**All treated (mITT) Cohort 1 + 2 (N = 101)**
ORR (%) [95% CI]	66 (56, 75)	72 (62, 81)
CR (%)	47	51
Duration of Response[a], median (range) in months	14.0 (0.0, 17.3)	14.0 (0.0, 17.3)
Duration of Response[a], CR, median (range) in months	NE (0.4, 17.3)	NE (0.4, 17.3)
Overall Survival, median (months) [95% CI]	17.4 (11.6, NE)	NE (12.8, NE)
6 month OS (%) [95% CI]	81.1 (72.5, 87.2)	79.2 (69.9, 85.9)
9 month OS (%) [95% CI]	69.4 (59.9, 77.0)	69.3 (59.3, 77.3)
12 month OS (%) [95% CI]	59.3 (49.6, 67.8)	60.4 (50.2, 69.2)

NE= Not estimable (not reached)
[a]Duration of response was censored at the time of SCT for subjects who received SCT while in response
Note: Median follow up time 15.1 months.

Table 13. Duration of Response Among Subjects with a Best Response of CR per central review (mITT Analysis Set)

	Cohort 1 (N = 37)	**Cohort 2 (N = 15)**	**Phase 2 Overall (N = 52)**
Duration of Response			
No. of subjects	37	15	52
Censored (%)	22 (59)	12 (80)	34 (65)
KM Median (95% CI) DOR time (in month)	14.0 (9.4, NE)	NE (11.3, NE)	NE (11.1, NE)
Type of Events			
Disease Progression	12	3	15
Disease/treatment related Death	3	0	3
Censoring reason			
Response ongoing	22	12	34
KM Estimate (95% CI) at			
3 Month	89.2 (73.7, 95.8)	100.0 (NE, NE)	92.3 (80.8, 97.0)
6 Month	75.2 (57.6, 86.2)	100.0 (NE, NE)	82.4 (69.0, 90.5)
9 Month	68.9 (50.8, 81.5)	93.3 (61.3, 99.0)	76.1 (61.7, 85.7)
12 Month	57.5 (38.3, 72.7)	72.7 (34.9, 90.8)	61.8 (45.0, 74.9)
Median Follow-up Time (in months) for DOR (reverse KM approach)	11.3 (10.8, 14.0)	11.3 (10.9, 14.2)	11.3 (11.0, 14.0)

Figure 8 DOR Using Investigator Assessment Cohorts 1 and 2 Combined (mITT Analysis Set; N = 83)

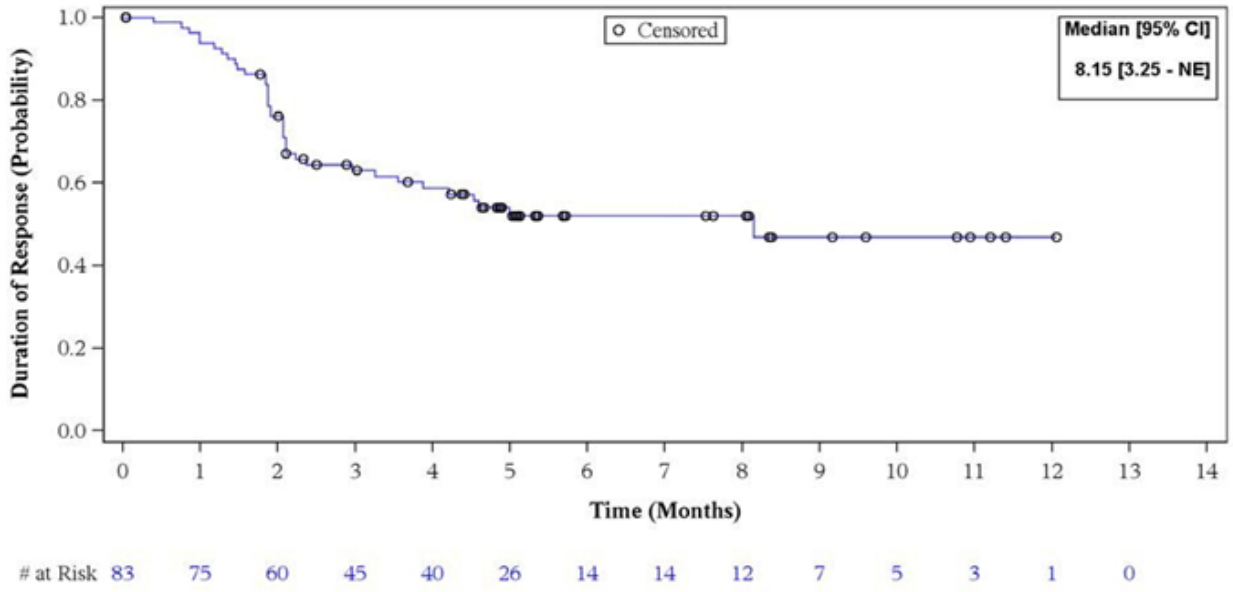


Figure 9. Duration of Response Among Subjects with a Complete Response or Partial Response for Cohorts 1 and 2 Combined (mITT Analysis Set; N = 83):

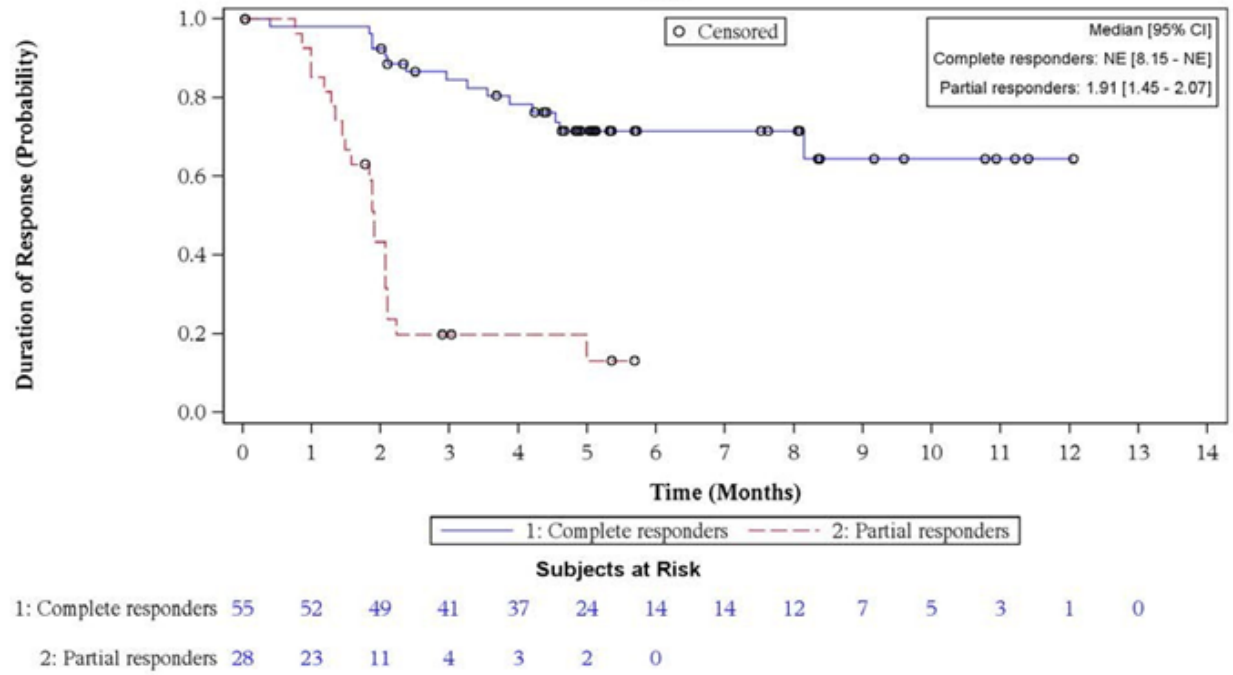
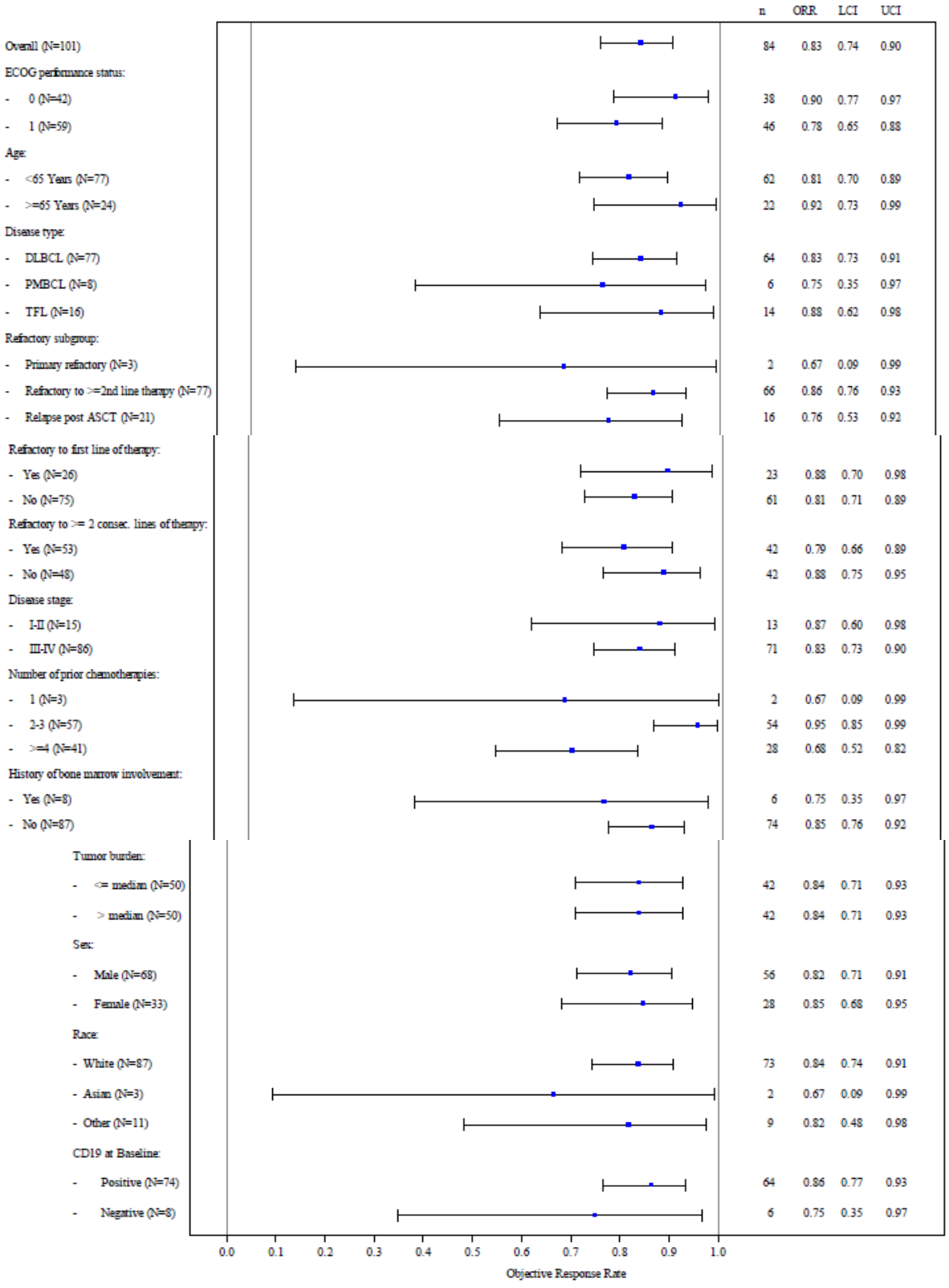


Figure 10 Subgroup Analysis of ORR in Phase 2 (Cohorts 1 and 2 Combined; mITT Analysis Set)



The median PFS based on the central review was 9.5 months in the Full Analysis Set. Kaplan–Meier estimates of PFS at 6, 9, and 12 months were 60.8%, 51.1% and 43.1%.

Table 14. Progression Free Survival Using Central Review (Full Analysis Set)

	Cohort 1 (N = 81)	Cohort 2 (N = 30)	Phase 2 Overall (N = 111)
Progression-free Survival (PFS)			
No. of subjects	81	30	111
Censored (%)	28 (35)	15 (50)	43 (39)
KM Median (95% CI) PFS time (in month)	7.3 (5.2, 12.4)	12.9 (4.5, NE)	9.5 (6.1, 12.9)
Type of Events			
Disease Progression	37	7	44
Disease/treatment related Death	16	8	24
Censoring reason			
Response/SD Ongoing	25	13	38
Started new anti-cancer therapy	2	0	2
Response not yet assessed	1	2	3
PFS (95% CI) at			
3 Month	82.5 (72.2, 89.2)	71.4 (50.9, 84.6)	79.6 (70.7, 86.1)
6 Month	58.3 (46.6, 68.2)	67.9 (47.3, 81.8)	60.8 (50.9, 69.3)
9 Month	46.3 (34.9, 56.9)	64.3 (43.8, 78.9)	51.1 (41.2, 60.2)
12 Month	39.3 (28.3, 50.0)	53.6 (33.8, 69.8)	43.1 (33.4, 52.3)

The median OS was 17.4 months (95% CI: 11.6, NE) in the Full Analysis set. Kaplan–Meier estimates of OS at 6, 9, 12 and 18 months were 81.1%, 69.4%, 59.3% and 48.8% in Cohorts 1 and 2 combined. The median OS in complete responders was not reached, was 7.7 months in partial responders and was 4.9 months in non-responders (based on the mITT set).

Table 15. Overall Survival (Full Analysis Set)

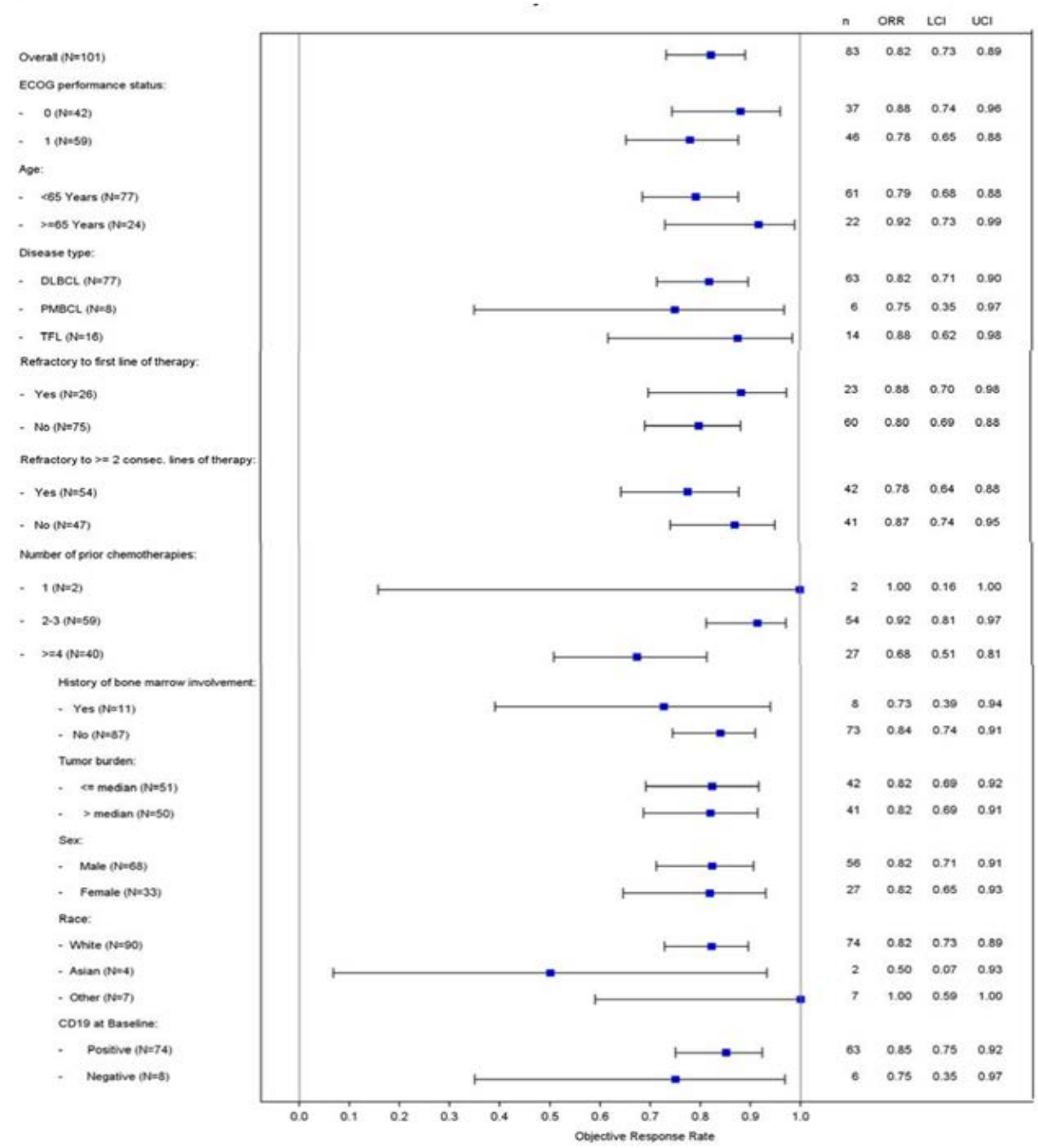
	Cohort 1 (N = 81)	Cohort 2 (N = 30)	Phase 2 Overall (N = 111)
Overall Survival (OS)			
No. of subjects	81	30	111
Censored (%)	39 (48)	20 (67)	59 (53)
KM Median (95% CI) OS time (in month)	15.4 (11.1, NE)	NE (10.9, NE)	17.4 (11.6, NE)
OS (95% CI) at			
3 Month	95.1 (87.4, 98.1)	80.0 (60.8, 90.5)	91.0 (83.9, 95.0)
6 Month	81.5 (71.2, 88.4)	80.0 (60.8, 90.5)	81.1 (72.5, 87.2)
9 Month	66.7 (55.3, 75.8)	76.7 (57.2, 88.1)	69.4 (59.9, 77.0)
12 Month	56.8 (45.3, 66.7)	66.2 (46.3, 80.2)	59.3 (49.6, 67.8)
15 Month	51.8 (40.4, 62.0)	66.2 (46.3, 80.2)	55.5 (45.8, 64.3)
18 Month	42.6 (28.8, 55.6)	66.2 (46.3, 80.2)	48.8 (37.3, 59.4)

Additionally, based on all 101 treated subjects, the response rate with axicabtagene ciloleucel showed no significant differences across subsets based on age (< 65 vs ≥ 65 years), NHL subset (DLBCL, PMBCL, or TFL); or refractory subgroup (refractory to primary or later line of therapy or relapsed within 12 months of ASCT).

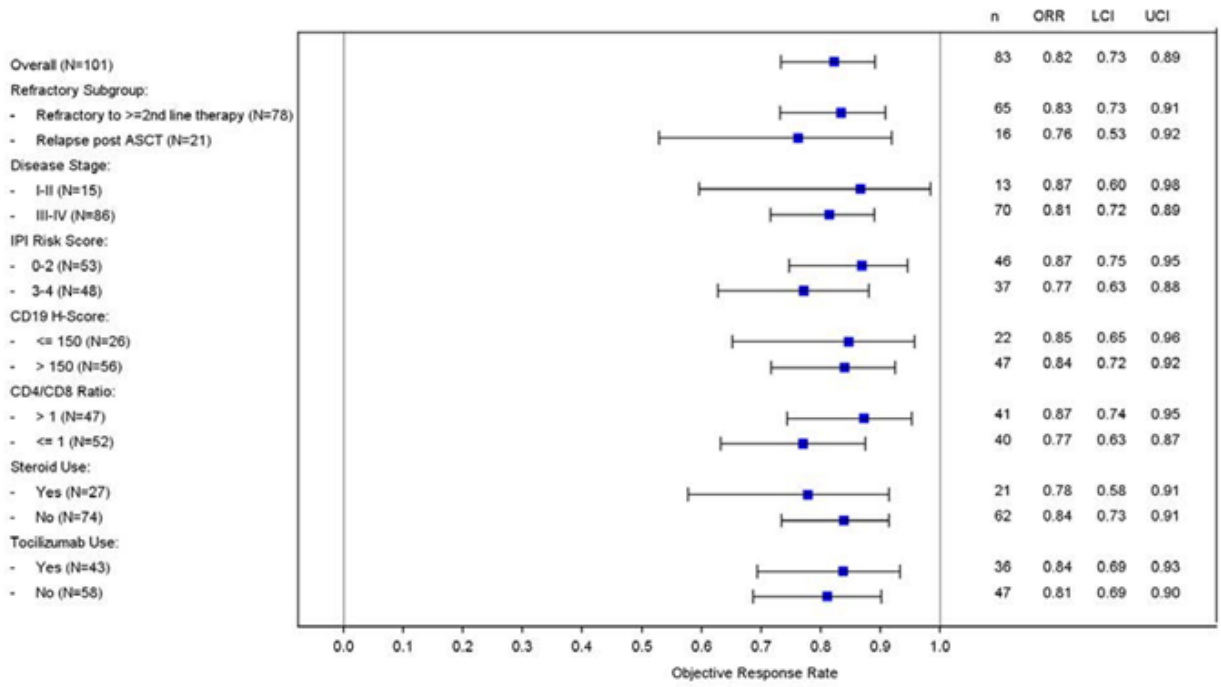
Ancillary analyses

Figure 11, Subgroup Analysis of Objective Response Rate in Phase 2 Cohorts 1 and 2 Combined (mITT Analysis Set)

PART A



PART B



LCI and UCI are the lower and upper limits of the 95% confidence interval of ORR using Chopper-Pearson Method.

Summary of main study

The following tables summarise the efficacy results from the main studies ZUMA-1 phase 2 and SCHOLAR-1 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 16: Summary of efficacy for trial ZUMA-1 phase 2

Title: A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)		
Study identifier	KTE-C19-101	
Design	ZUMA-1 is a single-arm, non-randomized, multicenter, open-label phase 2 study conducted to evaluate efficacy of axicabtagene ciloleucel in subjects with refractory aggressive forms of NHL, specifically DLBCL, PMBCL, and follicular lymphoma transformed to DLBCL (hereafter referred to as a transformed follicular lymphoma [TFL]). Subjects with refractory DLBCL were enrolled into Cohort 1 and subjects with refractory PMBCL or refractory TFL into Cohort 2. Key eligibility criteria were prior therapy including anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen; no central nervous system (CNS) lymphoma; no history of allogeneic SCT; no prior anti-CD19, CAR, or other genetically modified T-cell therapy.	
	Duration of main phase:	First subject enrolled in Phase 1: 21 Apr 2015
	Duration of Enrolment:	Ongoing in cohort 4

Hypothesis	ZUMA-1 phase 2 is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the ORR to KTE-C19 in cohorts 1 and cohort 2combined is significantly greater than 20%		
Treatments groups	Phase 2: cohort 1 and 2 (overall)		111 subjects enrolled 103 subjects treated with chemotherapy 101 subjects treated with Yescarta 77 patients in cohort 1 (with DLBCL), 24 patients in cohort 2 (with PMBCL, TFL)
Endpoints and definitions	Primary endpoint	ORR	Objective response rate defined as a CR or PR per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by study investigators
	Secondary Endpoints	DOR	Duration of response based on Kaplan-Meier estimate; according to the investigator's assessment, and by central review, both based on IWG 2007 criteria (Cheson et al, 2007).
		PFS	Progression Free Survival time based on Kaplan-Meier estimate; according to the investigator's assessment, and by central review, both based on IWG 2007 criteria (Cheson et al, 2007).
		OS	Overall Survival based on Kaplan-Meier estimate
		CR	Complete response per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheeson 2007) as determined by study investigators
Database lock	11 August 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified intent to treat (all treated patients)		
Descriptive statistics and estimate variability	Treatment group	Cohort 1 (DLBCL) *Interim Analysis 2*	Cohort 1 + 2 (DLBCL/PMBCL/TFL) *Primary analysis*
	Number of subject	N = 51	N = 92
	ORR (Responder)	76% (n = 39)	82% (n = 75)
	95% CI (Clopper-Pearson)	(63%, 87%)	(72%, 89%)
Effect estimate per comparison	Primary endpoint Cohort 1	Comparison groups	ORR vs 20% historic ORR
		P-value	< 0.0001
	Primary endpoint Cohort 1 + 2	Comparison groups	ORR vs 20% historic ORR

		P-value		< 0.0001
Notes	Both endpoints were met (taking multiplicity adjustment into account). The primary confirmatory analyses were based on subsets of the data only (IA2 for Cohort 1, n = 51; N = 92 for Cohort 1 + 2). All further analyses are based on all enrolled patients to provide a better understanding and better estimates for the observed treatment effects.			
Analysis description	**Secondary analyses (12 months update; Data cutoff: 11 Aug 2017): ITT population**			
Descriptive statistics and estimate variability	Treatment group	Cohort 1 (DLBCL)	Cohort 2 (PMBCL/TFL)	Cohort 1 + 2
	Number of subject	N = 81	N = 30	N = 111
	ORR [% (n), 95% CI]	79% (n = 64) (69%, 87%)	73% (n = 22) (54%, 88%)	77% (n = 86) (69%, 85%)
	ORR (**central**) [% (n), 95% CI]	64% (n = 52) (53%, 75%)	70% (n = 21) (51%, 85%)	66% (n = 73) (56%, 75%)
	CR [% (n)]	51% (n = 41)	67% (n = 20)	55% (n = 61)
	CR (**central**) [% (n)]	46% (n = 37)	50% (n = 15)	47% (n = 52)
	PFS [median, 95% CI; in months]	6.0 (3.9, 8.1)	13.7 (3.0, NE)	6.3 (4.0, 12.7)
	PFS (**central**) [median, 95% CI; in months]	7.3 (5.2, 12.4)	12.9 (4.5, NE)	9.5 (6.1, 12.9)
	OS [median, 95% CI; in months]	15.4 (11.1, NE)	NE (10.9, NE)	17.4 (11.6, NE)
	DOR [n, median, 95% CI; in months]	N = 64 5.0 (2.1, NE)	N = 22 NE (11.1, NE)	N = 86 11.1 (4.2, NE)
	DOR (**central**) [n, median, 95% CI; in months]	N = 52 10.9 (5.4, NE)	N = 21 NE (11.1, NE)	N = 73 14.0 (8.3, NE)
Analysis description	**Secondary analyses (12 months update; Data cutoff: 11 Aug 2017): mITT population**			
Descriptive statistics and estimate variability	Treatment group	Cohort 1 (DLBCL)	Cohort 2 (PMBCL/TFL)	Cohort 1 + 2
	Number of subject	N = 77	N = 24	N = 101
	ORR [% (n), 95% CI]	83% (n = 64) (73%, 91%)	83% (n = 20) (63%, 95%)	83% (n = 84) (74%, 90%)
	ORR (**central**) [% (n), 95% CI]	68% (n = 52) (56%, 78%)	88% (n = 21) (68%, 97%)	72% (n = 73) (62%, 81%)
	CR [% (n)]	53% (n = 41)	75% (n = 18)	58% (n = 59)
	CR (**central**) [% (n)]	48% (n = 37)	63% (n = 15)	51% (n = 52)
	PFS [median, 95% CI; in months]	5.1 (3.0, 9.1)	NE (3.7, NE)	5.9 (3.3, NE)
	PFS (**central**) [median, 95% CI; in months]	6.9 (4.5, 11.8)	12.5 (9.0, NE)	9.1 (5.8, 12.5)

	OS [median, 95% CI; in months]	15.4 (10.4, NE)	NE (NE, NE)	NE (12.8, NE)
	DOR [n, median, 95% CI; in months]	N = 64 5.0 (2.1, NE)	N = 20 NE (11.1, NE)	N = 84 11.1 (3.9, NE)
	DOR (**central**) [n, median, 95% CI; in months]	N = 52 10.9 (5.4, NE)	N = 21 NE (11.1, NE)	N = 73 14.0 (8.3, NE)
Notes	NE = Not evaluable			

Analysis performed across trials (pooled analyses and meta-analysis)

Scholar-1

SCHOLAR-1 is a patient pooled, retrospective analysis, which integrated data from 2 randomized Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational databases (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence [SPORE]) of patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL), with refractory defined as progressive disease (PD) or stable disease (SD) < 6 months as best response to last line of chemotherapy (≥ 4 cycles of first-line or 2 cycles of later-line therapy) or relapse ≤ 12 months after autologous stem cell transplantation (ASCT).

Table 17 Databases Contributing to SCHOLAR

Institution	Database Type	Data Abstraction Criteria	Outcomes Collected
MDACC	Retrospective database	Identify subjects with: • Best response of PD to second-line therapy • Best response of SD to second-line therapy after at least 2 treatment cycles • Relapse within 1 year of ASCT	Response to salvage therapy Survival
NCIC	Subset of a randomized clinical trial	Extract a subset of data from the randomized, multicenter, Phase 3 Ly.12 study[a]. Identify subjects with: • Best response of PD to first-line therapy • Best response of SD to first-line therapy after at least 4 treatment cycles • Best response of PD to second-line therapy given in Ly.12[a] • Best response of SD to second-line therapy given in Ly.12[a] after at least 2 treatment cycles • Relapse within 1 year of ASCT	Response to second-line salvage therapy Survival
Mayo/Iowa (Specialized Program of Research Excellence [SPORE] Lymphoma Database)	Retrospective database	Identify subjects with: • Best response of PD to any line therapy • Best response of SD to first-line therapy after at least 4 treatment cycles of therapy • Best response of SD to later-line (> 1) therapy after at least 2 cycles of therapy • Relapse within 1 year of ASCT	Response to salvage therapy Survival
CORAL	Subset of randomized clinical trails	Extract a subset of data from the randomized, multicenter, Phase 3 CORAL study[b]. Identify subjects with: • Best response of PD to first-line therapy • Best response of SD to first-line therapy after at least 4 treatment cycles	Response to second-line salvage therapy Response to third-line salvage therapy Survival

Institution	Database Type	Data Abstraction Criteria	Outcomes Collected
		• Best response of PD to second-line therapy given in Ly.12 • Best response of SD to second-line therapy given in Ly.12 after at least 2 treatment cycles • Relapse within 1 year of ASCT	

4 Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem Cell

Study participants

The data set evaluated outcomes in patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL), with refractory defined as progressive disease (PD) or stable disease (SD) < 6 months as best response to last line of chemotherapy (≥ 4 cycles of first-line or 2 cycles of later-line therapy) or relapse ≤ 12 months after autologous stem cell transplantation (ASCT).

Among 861 patients, 636 were included based on the refractory search criteria.

Table 18 Search criteria used to define the SCHOLAR-1 study population

Patient/Treatment Characteristic	Included If	Additional Specification
Patient characteristics – All patient characteristic conditions must be met		
Disease type	Disease type is DLBCL, PMBCL, or follicular lymphoma (FL after initial diagnosis and treatment)	DLBCL only
Diagnosis date	≥ 01 Jan 2000	
Chemo-refractory status – One of the following chemo-refractory status conditions must be met		
Response to prior therapy	Included if stable disease (SD) or progressive disease (PD) at time of enrollment into CORAL	
Disease status after ASCT	Disease status is progressed or recurred within 12 months of ASCT	
Salvage chemotherapy treatment – All of the salvage chemotherapy treatment conditions must be met		
Treatment	Treated with salvage chemotherapy after determination of chemo-refractory status	
Allogeneic stem cell transplantation	None prior to treatment with salvage chemotherapy	

Main inclusion criteria:

For the subject level data, subjects were included in outcome analyses if they were determined to be refractory and had commenced the next line of systemic therapy for refractory disease. Refractory disease was defined as one of the following: PD as best response to any line of chemotherapy; SD as best response to ≥ 4 cycles of first-line or 2 cycles of later-line therapy; or relapse ≤ 12 months following ASCT. Subjects must have received an anti-CD20 mAb, such as rituximab (unless disease was CD20^{-}), and an anthracycline

as one of their prior regimens. Subjects with central nervous system (CNS) disease, and with year of diagnosis prior to 2000 were excluded. Kite reviewed the abstraction results and programmatically identified the subset of subjects who could be documented to meet all elements of the refractory definition used. Upon abstraction, subjects were further classified into refractory category subgroups based on the first time in the treatment course that a subject met the criteria for refractory status. These refractory category subgroups were primary refractory, refractory to second or later line therapy, and relapse ≤ 12 months of ASCT.

Treatments

All evaluated patients received standard-therapies.

Objectives

Primary Objective:

The primary objective is to estimate the RR and complete response rate among subjects with refractory DLBCL, TFL, and PMBCL when treated with salvage chemotherapy (currently available standard of care).

These estimated RR from Scholar-1 should be compared with the ORR observed in the ZUMA-1 primary analysis.

Secondary Objective:

The secondary objective is to estimate overall survival among subjects with refractory DLBCL, TFL, and PMBCL when treated with salvage chemotherapy (with currently available standard of care).

This estimated OS in patients with refractory DLBCL, TFL, and PMBCL in SCHOLAR-1 should be compared with OS of subjects in the ZUMA-1 primary analysis.

Outcomes/endpoints

The endpoints in SCHOLAR-1 were RR, complete response rate (CRR), and OS.
For the 2 randomized studies included in SCHOLAR-1, response to therapy for refractory disease was according revised International Working Group (IWG) Response Criteria for Malignant Lymphoma as assessed by the investigator (hereafter referred to as IWG 1999 criteria). For the 2 retrospective databases, response was according to investigator assessment (assessment criteria not available). Subjects were evaluable for response if they had been determined to be refractory, had commenced therapy for refractory disease, and had evidence of response assessment (a date of assessment and an assessment outcome other than "Not Done") after commencement of therapy. The latter condition was included in order to avoid underestimating the response rate by the inclusion of subjects receiving only palliative care after the determination of refractory disease. Survival was measured from the commencement of treatment for refractory disease to death or date last known alive.

Sample size

No sample size calculations were performed. All patients eligible were analysed.

Randomisation

Not applicable as this was a retrospective single arm patient-level meta-analysis.

Blinding (masking)

Not applicable as this was a retrospective single arm patient-level meta-analysis.

Statistical methods

The SCHOLAR-1 study serves as historic control. Higgin's Q statistic (Higgins, 2002) was used to assess evidence of heterogeneity in response rate among institutions. If the p-value from this test was > 0.10, data from the 4 institutions were to be combined to estimate the RR and 95% CI. A random effects model (DerSimonian & Laird, 1986) was used to estimate the RR and CI, considering institution as a random effect. Summaries presented the RRs and 95% CIs by institution and based on the result of the Higgin's Q test overall. OS was analysed using the Kaplan-Meier (KM) method. KM plots, the median survival time (95% CI), and the survival rate at 2 years was to be estimated by institution and overall in the survival analysis set.

Results

The SCHOLAR-1 data set comprised 636 subjects identified from a total pooled population of 861 subjects with refractory aggressive B-cell NHL (DLBCL, PMBCL, and TFL) from 2 randomized clinical trials and 3 academic center databases, who correspond to the ZUMA-1 population. Based on the Scholar-1-evaluable set, 636 were identified with aggressive B-cell lymphoma. The majority of patients had DLBCL (88%) and a median age of 55 of patients. 58% had a history of primary refractory disease, 20% received the salvage therapy for primary refractory disease, 62% were refractory to at least two prior lines of therapy and 18% had a relapse after ASCT within 12 month. The primary analyses of response and OS comprised 523 subjects and 603 subjects, respectively.

Table 19 SCHOLAR-1 Data Abstraction and Analysis Sets

Analysis Set1	ZUMA-1	SCHOLAR-1
All abstracted – n	NA	861
First Refractory Categorization		
SCHOLAR-1-evaluable	NA	636
RR-evaluable	NA	523
Survival-evaluable	NA	603
Survival-RR-	NA	513
Last Refractory Categorization		
RR-evaluable	101	508
Survival-evaluable	101	497

Table 20: Baseline demographics and disease characteristics.

		SCHOLAR-1	
	ZUMA-1 mITT (N = 101)	Response (N = 508)	Survival (N = 497)
Sex			
N	101	508	497
Female	33 (33)	181 (36)	176 (35)

		SCHOLAR-1	
	ZUMA-1 mITT (N = 101)	Response (N = 508)	Survival (N = 497)
Male	68 (67)	327 (64)	321 (65)
Age (years)			
N	101	508	497
Median (Min, Max)	58.0 (23, 76)	55.0 (19, 81)	55.0 (19, 81)
<65 Years	77 (76)	434 (85)	428 (86)
>=65 Years	24 (24)	74 (15)	69 (14)
ECOG [a]			
N	101	288	281
0-1, n (%)	101 (100)	230 (80)	226 (80)
2-4, n (%)	0	58 (20)	55 (20)
Not Assessed	0	220	216
IPI Score [a]			
N	101	215	215
0 – 1, n (%)	27 (27)	73 (34)	73 (34)
2, n (%)	26 (26)	66 (31)	66 (31)
>= 3, n (%)	48 (48)	76 (35)	76 (35)
Not Assessed	0	293	282
Disease Stage [a]			
N	101	224	224
I-II, n (%)	15 (15)	75 (33)	75 (33)
III-IV, n (%)	86 (85)	149 (67)	149 (67)
Not Assessed	0	284	273
Disease Type			
N	101	508	497

		SCHOLAR-1	
	ZUMA-1 mITT (N = 101)	Response (N = 508)	Survival (N = 497)
DLBCL, n (%)	77 (76)	447 (88)	436 (88)
TFL / PMBCL, n (%)	24 (24)	20 (4)	20 (4)
Other, n (%)	0	35 (7)	35 (7)
Missing, Indeterminate, or Unknown, n (%)	0	6 (1)	6 (1)
Region			
N	101	508	497
Europe/Israel, n (%)	1 (1)	170 (33)	170 (34)
North America, n (%)	100 (99)	338 (67)	327 (66)
Data Source			
N	101	508	497
Clinical Trial, n (%)	101 (100)	262 (52)	262 (53)
Retrospective Database, n (%)	0	246 (48)	235 (47)
Total Number of Lines of Chemotherapy & ASCT Received [b]			
N	101	417	410
1, n (%)	2 (2)	101 (24)	100 (24)
2, n (%)	29 (29)	206 (49)	204 (50)
3, n (%)	30 (30)	94 (23)	91 (22)
4, n (%)	28 (28)	12 (3)	11 (3)
5, n (%)	6 (6)	1 (0)	1 (0)
>5, n (%)	6 (6)	3 (1)	3 (1)
Not Assessed	0	91	87
Refractory Subgroup			
N	101	508	497
Primary refractory, n (%)	2 (2)	101 (20)	100 (20)
Refractory to 2nd or Later Line, n (%)	78 (77)	316 (62)	310 (62)

		SCHOLAR-1	
	ZUMA-1 mITT (N = 101)	Response (N = 508)	Survival (N = 497)
Relapse within 12 Months of ASCT, n (%)	21 (21)	91 (18)	87 (18)
Ever Primary Refractory			
N	101	508	497
No, n (%)	75 (74)	277 (55)	267 (54)
Yes, n (%)	26 (26)	231 (45)	230 (46)
Refractory to at least 2 consecutive lines of therapy			
N	101	508	497
No, n (%)	47 (47)	193 (38)	187 (38)
Yes, n (%)	54 (53)	315 (62)	310 (62)
Autologous or allogeneic transplant at any time after determination of refractory status			
N	101	508	497
No, n (%)	90 (89)	347 (68)	336 (68)
Yes, n (%)	11 (11)	161 (32)	161 (32)

Abbreviations: IPI, international prognostic index; ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplant; DLBCL, diffuse large B cell lymphoma; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma

Table 21 Response and CRRs

	ZUMA-1 (N = 101)	CORAL (N = 170)	LY12 (N = 219)	MAYO (N = 82)	MDACC (N = 165)	Overall (N = 636)
Response Rate to subsequent therapy [a]						
n	101	170	106	82	165	523
Responders, n (%)	83 (82)	53 (31.2)	28 (26.4)	21 (25.6)	33 (20.0)	135 (25.8)
95% Exact CI	(73, 89)	(24.3, 38.7)	(18.3, 35.9)	(16.6, 36.4)	(14.2, 26.9)	(22.1, 29.8)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	25.7 (20.9, 31.3)
Complete Response Rate to subsequent therapy [a]						
n	101	170	106	82	165	523
Responders, n (%)	55 (54)	26 (15.3)	2 (1.9)	6 (7.3)	11 (6.7)	45 (8.6)
95% Exact CI	(44, 64)	(10.2, 21.6)	(0.2, 6.6)	(2.7, 15.2)	(3.4, 11.6)	(6.3, 11.3)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	7.0 (3.2, 14.5)
Partial Response Rate to subsequent therapy [a]						
n	101	170	106	82	165	523
Responders, n (%)	28 (28)	27 (15.9)	26 (24.5)	15 (18.3)	22 (13.3)	90 (17.2)
95% Exact CI	(19, 38)	(10.7, 22.3)	(16.7, 33.8)	(10.6, 28.4)	(8.5, 19.5)	(14.1, 20.7)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	17.5 (13.3, 22.7)

The secondary endpoint was OS, DOR was not assessed. Among 603 subjects evaluable for OS, the median OS was 6.3 months. The, 6-month and 1- and 2-year survival rates were 53%, 28% and 20%. Subgroup analyses of OS indicate that survival is poor in all evaluated subgroups. Consistent with the literature review, median OS was less than 10 months in all subgroups except those who underwent SCT after being determined to be refractory.

Standardized analyses of response and survival were undertaken to address these potential imbalances. Two covariates were specified for use in the standardization: last refractory subgroup and the occurrence of SCT at any time after determination of refractory status. Results of the standardized analysis showed a RR of 20% (15%, 25%) and a median OS of 3.9 months in SCHOLAR-1. The standardized analyses suggested odds ratios for ZUMA-1: SCHOLAR-1 of approximately 3.8 for RR and 8 for CR. Standardized analyses of OS showed 6-month and 1-year survival rates of 77% and 52%, respectively for subjects in ZUMA-1 compared with 35% and 17%, respectively, for subjects in SCHOLAR-1 and a 77% reduction in the overall risk of death for subjects in ZUMA-1 relative to SCHOLAR-1. These standardized results are considered to confirm a response rate of approximately 20% for subjects with refractory aggressive NHL treated with currently available therapies and support the primary SCHOLAR analysis.

Exploratory endpoints

One subject (1%) in Cohort 1 and 2 subjects (8%) in Cohort 2 underwent allogeneic SCT while in response (2 in PR; 1 in CR) after axicabtagene ciloleucel treatment, and no subjects underwent ASCT after responding to the initial axicabtagene ciloleucel infusion.

A total of 9 subjects were retreated with Yescarta in Phase 2. Based on the investigator's assessment, 5 of 9 retreated subjects responded (2 CR and 3 PR) at Month 1. Analysis of duration of retreatment response (DORR) among the retreated subjects in Phase 2 showed a median DORR of 3.5 months as of the data cut-off date. Results were identical in a sensitivity analysis that excluded responses that occurred after ASCT following retreatment in 4 subjects. One subject underwent ASCT and 3 subjects underwent allogeneic SCT. Three of the 4 subjects underwent transplant while in response (2 in PR; 1 in CR). Two subjects were still in response at data cutoff, including 1 subject who had undergone allogeneic SCT. None of the subjects who were retreated converted from SD or PR to PR or CR.

Change in tumour burden was measured by baseline SPD of selected nodes or lesions from baseline to the post-baseline nadir, per investigator measurements. The median percent change from baseline in SPD at 6 months, 9 months, and 12 months were -87%, -92%, and -100%, respectively, in Cohorts 1 and 2 combined; and -84%, -96%, and -100% for Cohort 1.

Table 22: Summary of efficacy for trial SCHOLAR-1:

Title: Outcomes in Refractory Aggressive B-cell Non-Hodgkin Lymphoma: Results from the International SCHOLAR-1 Study			
Study identifier	Scholar-1		
Design	Retrospective meta-analysis. Data from 2 randomized Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational databases (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence [SPORE]) are integrated. The study is sourced from the databases of 3 academic centers and from 2 of the largest randomized, controlled phase 3 trials of patients with relapsed/refractory aggressive lymphomas, including DLBCL, TFL and PMBCL. Key eligibility criteria were highly chemo-refractory aggressive B-cell Non-Hodgkin-Lymphoma, chemo-refractory disease, no history of allogeneic SCT.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		N/A N/A N/A
Hypothesis	Estimation		
Treatments groups	Standard therapies		Patients received standard therapies, not further specified, N=861.
Endpoints and definitions	Primary endpoint	RR	Response rate (not objective response)
	Secondary endpoint	OS	Overall survival time (KM-Estimator)
		CR	Complete response
Database lock	unknown		
Results and Analysis			

Analysis description	**Primary Analysis**	
Analysis population and time point description	Scholar-1 evaluable set (n = 636), RR-evaluable set (n = 523), Survival set (n = 603), RR/Survival set (n = 513)	
Descriptive statistics and estimate variability	Number of subjects	N = 636
	RR (DerSimonian-Laird Estimator)	25.7%
	95% CI	(20.9%, 31.3%)
	CR (DerSimonian-Laird Estimator)	7.0%
	95% CI	(3.2%, 14.5%)
	Number of subjects	N = 603
	OS (median, in months)	6.3
	95% CI	(5.9, 7.0)
Notes	Retrospective studies included in estimates; Additional standardized analysis was conducted post-hoc and is considered supportive only.	

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	N/A		
Non Controlled Trials	23/108	4/108	0/108

Supportive studies

NCI 09-C-0082

Thirteen subjects with DLBCL, TFL, or PMBCL were enrolled in Cohorts 11 through 14 and received conditioning chemotherapy and the anti-CD19 CAR T cell infusion. In the NCI study, subjects were not followed for survival after disease progression. Six subjects withdrew from the study; 4 had disease progression, 1 withdrew consent, and 1 was withdrawn at the investigator's discretion; 7 subjects remain in follow-up as of 10 Nov 2016. All but 1 subject treated in Cohorts 11 through 14 received 2 x 10^6 cells/kg (1 subject received 6 x 10^6 cells/kg and experienced DLTs). The median age of this population was 52 years (range: 29 to 68 years); most subjects (84.6%) were male, and all were white. Ten of the 13 subjects had DLBCL (76.9%), 2 had PMBCL (15.4%), and 1 had TFL (7.7%). Subjects received a median of 4 prior regimens, all subjects had received an anthracycline and an anti-CD20 agent, and 11 subjects (84.6%) received a platinum-based agent. Eight subjects (61.5%) were chemo-refractory and 3 subjects (23.1%) had relapsed after receiving ASCT. Two subjects with DLBCL had relapsed, transplant-ineligible disease. All 13

treated subjects underwent post-treatment assessments for disease response as defined by IWG 2007 criteria (Cheeson et al, 2007).

Table 23: Objective tumour response in NCI 09-C-0082

	Subjects with DLBCL, PMBCL, and TFL[1] (N = 13)
Objective response rate, n (%)	9 (69.2)
95% CI (Clopper-Pearson)	38.6, 90.9
Complete	8 (61.5)
Partial	1 (7.7)
Stable	2 (15.4)
Progression	2 (15.4)
Not evaluable	0

As of the data cutoff date for this report, median follow-up time for the 9 subjects who achieved an objective response was 9.4 months. All 9 subjects remained in response, and the longest ongoing response was 18+ months. Median duration of response was 8.8 months (range: 3 to 18 months). At a median follow-up time of 9.4 months, the median PFS interval had not been reached. In the OS analysis, 10 subjects were still alive. The 3 subjects who died included the 2 subjects with disease progression as best response, and 1 subject who progressed and died after having SD for approximately 2 months. Median OS has not been reached. An update of DOR (10 November 2016) showed that the Kaplan-Meier median DOR had not been reached (range: 2.8+ to 23+ months).

Due to the small number of subjects in this group, analysis of response across subsets was not possible. The results in this subset were consistent with the overall results for the NCI study. As of 10 November 2016, the ORR for the entire study population of 43 subjects was 74%, with a CR rate of 54% and a PR rate of 21%. Twenty-one of the 43 subjects (49%) were still in response, with a median follow-up of 36 months (range: 13 to 78 months). Median duration of response was 35 months (range: 2.8+ to 77 months). Nineteen subjects (44%) had ongoing responses for more than 1 year. Twenty of the 43 subjects (47%) were still in CR, with a median follow-up of 31 months (range: 13 to 65 months). Eighteen subjects (42%) had an ongoing CR for more than 1 year.

ZUMA-1 phase 1

Table 24: Summary of Best Overall Response (Phase 1)

Response Category	Phase 1 (N = 7) n (%)
Number of Objective Responders (CR + PR)	5 (71)
Complete Response (CR)	4 (57)
Partial Response (PR)	1 (14)
Stable Disease	1 (14)
Progressive Disease	0 (0)
Not Evaluable	0 (0)
Not Done (ND)	1 (14)

Most subjects in Phase 1 and Phase 2 had stage III-IV disease, were refractory to second or greater line therapy, and had medium-high to high risk IPI scores. In Phase 1, the median age was 59 years (range: 29 to 69 years); 71% of subjects were male and 86% were white. In Phase 2, the median age was 58 years (range: 23 to 76 years); most subjects (67%) were male, and 89% were white.

Phase 1 identified a tolerable regimen for further study in Phase 2. Seven of 8 leukapheresed subjects received low-dose conditioning chemotherapy (cyclophosphamide 500 mg/m2 and fludarabine 30 mg/m2) followed by a single infusion of axicabtagene ciloleucel at 2 x 10^6 anti-CD19 CAR T cells/kg.

The ORR according to the investigator's assessment was 71% (5 responders among 7 subjects). All 5 subjects who had a response achieved the response within 1 month after infusion of axicabtagene ciloleucel. The 5 responders comprised 4 subjects (57%) with a CR and 1 subject (14%) with a PR. Among the 5 subjects who achieved an objective response, the median DOR was not reached; with a median (95% CI) follow-up time of 17.1 months (16.3, 17.4 months). Three subjects remained in ongoing CR at 18+ months.

Four responders had previously relapsed within 1 year of ASCT and 1 responder had been refractory to previous treatment. Among the 2 subjects who did not have an objective response, 1 had SD as a best response, and the other died prior to the first response assessment.

2.4.8. Discussion on clinical efficacy

Design and conduct of clinical studies

The main study for this application is KTE-C19-101 (ZUMA-1), an open-label single arm multicenter trial evaluating the safety and efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma, with supporting evidence coming from initial dose and regime finding NCI 09-C 0082 trial. Cohort 1 of ZUMA-1 phase 2 included 77 patients with DLBCL cohort 2 included 24 patients with either TFL or PMBCL and the ongoing cohort 3 53 patients, of which about 34 have already been treated. The cohort 3 of ZUMA-1 introduced revised CRS and neurotoxicity management algorithm including the prophylactic use of tocilizumab and levatiracetam as well as the reactive use of corticosteroids and was originally not intended to

support the primary analysis of ZUMA-1. Clinical studies have been conducted at 25 USA sites and 1 Israel site (Sourasky Medical Center). No EU sites have been involved.

Dose has been selected based on results of NCI Study 09C0082 aiming to achieve adequate lymphodepletion and therapeutic levels of anti-CD19 CAR T cells without intolerable toxicity. The same dosing of conditioning chemotherapy agents and axicabtagene ciloleucel was given in ZUMA-Phase-1 with the result of 1 DLT in altogether 6 DLT-evaluable subjects, which was considered as tolerable and effective dose. Hence, no lower dose-regimen for chemotherapy or axicabtagene ciloleucel was implemented for phase 2. The dose finding methodology used in NCI 09C-0082 and in Phase 1 part of the ZUMA-1 trial is considered generally acceptable.

In Phase 2 of ZUMA-1, of the 111 subjects undergone leukapheresis, 103 subjects (93%) were treated with conditioning chemotherapy and 101 (91%) were treated with Yescarta. With respect to the conduct of the ZUMA-1 phase 2 study, changes concerning particularly eligibility criteria of the target population have been implemented. While some of the changes are safety-related to improve prevention and management of AEs associated with CAR-T cells therapy, other changes concerned study design characteristics. These changes did not affect the integrity of the study.

Further, 19 protocol deviations in 17 patients of the mITT, population were detected. In most of these patients (12/17), the baseline-PET scan to ensure the diagnose was not performed within 28 days of conditioning chemotherapy, but within day -29 and -41 relative to conditioning chemotherapy, while none of these patients received anti-cancer therapy during the interval. Three patients received a compromised product, but all of them received the minimum dose of $1x10^6$ anti-CD19 CAR T cells/kg body weight and responded to therapy. With regard to 7 patients, who either received steroids within 7 days prior to leukapheresis (n=2) or within 5 days prior to infusion with Yescarta, the treatment ended 2-4 days before treatment with Yescarta in all cases.

Response determination utilized the IWG criteria with updated recommendations (the Lugano classification, Cheeson et al, 2014) for evaluation, staging and assessment of response in patients with NHL.

Assessment of Quality-of-life data was not included within the endpoints of ZUMA-1 phase 2; however, outcomes based on the European Quality of Life-5 Dimensions (EQ-5D) are being investigated in cohort 3 of ZUMA-1 (see RMP).

Efficacy data and additional analyses

Results of the ZUMA-1 phase 2 study indicated that a single dose of treatment with Axicabtagene ciloleucel at a target doses of 2×10^6 anti-CD19 CAR T cells/kg (+/- 20%) showed a high increase of ORR and a clearly better efficacy profile compared to the retrospective global patient-level pooled study (Scholar-1) in patients with aggressive forms of NHL, specifically DLBCL, PMBCL and transformed follicular lymphoma. Based on the refined estimation in the ITT-population, the ORR was 66% with a complete response rate of 47% and a partial response rate of 19% (central review). These data are substantiated by similar ORR in ZUMA-1 Phase 1 (71% ORR) and the subset of 13 subjects from NCI 09-C-0082 (69% ORR). Of note, the average remission rate of salvage therapy based on the SCHOLAR-1 results was about 25.7%. Despite limited follow up, durability of response is documented. For the 85% of patients with stage III/IV disease, efficacy assessment based on the central review showed lower values of ORR and time-dependent endpoints for patients in advanced disease stages (ORR: 69, CR: 45%) compared to stage I/II patients (ORR: 93%, CR: 45%), however a clear superiority compared to historical controls persists and no difference was shown with respect

to CR rates between patients with advanced disease vs stage I/II patients. For some patients disappearance of either B-symptoms (6/6 patients) or hepatomegaly (5/6 patients) could be shown.

Within ZUMA-1 phase 2, 101 of 111 patients who underwent leukapheresis received axicabtagene ciloleucel. While most of these patients had DLBCL (76%), 16% had TFL and 8% had PMBCL. All patients had a baseline ECOG-score of 0/1, the median number of prior therapies was 3 (range: 1 to 10), 2 patients received study treatment for primary refractory disease, 26% had a history of primary refractory disease, 77% were refractory to 2nd or later line of therapy and 21% had a relapse within 12 months following ASCT. Baseline patients and disease characteristics appear very consistent between ITT and mITT population. Since the overall treatment includes the leukapheresis, chemotherapy and IMP-administration, all enrolled patients need to be considered. Further, main analyses should reflect the objective response data of the central assessment and not be based on study investigators addressing that the concordance of both assessments was 70.4% and that the local assessment tended systematically towards better outcomes. Particularly concerning the open-label, single-arm study, efficacy assessment based on the central review assessment was clearly preferred for regulatory decisions to minimize bias.

By the data cut-off 11 August 2017, the ORR based on the mITT-analysis and investigator´s assessment was 83% (95%CI: 74% to 90%) with a CR rate of 58%, while the ORR based on the ITT-population and central review was 66% (95% CI: 56% to 75%) with a CR rate of 47%. These data showed that the response based on the ITT-population and further based on the central review was lower, however, the general magnitude of effect compared to the outcomes of SCHOLAR-1 remains.

While the estimated median DOR was 14 months, the estimated median DOR among all complete responders was not reached yet with an estimated median follow-up time of 11.3 months. The ORR based on the ITT population, central review and the 12 months update is consistent across cohorts in ZUMA-1: Cohort 1, 2 and combined (respectively Cohort 1: 64%, Cohort 2: 70%, combined 66%) and is also consistent with the NCI study (ORR: 69.2%) and ZUMA-1 Phase 1 (ORR: 71%).

ORRs and 95% CIs for the Phase 2 Cohorts 1 and 2 combined were further analysed by baseline demographic and disease characteristics, product characteristics, and use of tocilizumab and systemic steroids. Mean ORRs for each subset ranged from 67% to 99% and were comparable to the ORR for the Phase 2 population overall (83%) based on the mITT and investigator´s assessment. No significant impact of subsets based on age, sex, disease type (DLBCL, PMBCL, or TFL), and refractory subgroups, primary refractory status, refractory status to 2 or more consecutive lines of therapy, disease stage, IPI risk score, tumour burden, CD4:CD8 ratio of (> 1 or ≤ 1) and the use tocilizumab or steroids (yes or no) became apparent. Responses also were consistent in subjects whose tumours were retrospectively assessed as CD19+ (ORR = 85%) or CD19– (ORR = 75%). However, the small sample size limits the significance of this subgroup ORR analysis.

In view of addressing differences in view of morphology and histology, efficacy outcomes (ORR, CR, DOR, PFS and OS) were assessed for subjects with either TFL or PMBCL in a pooled dataset comprising cohorts 2 and 3 from phase 2 of ZUMA-1, using a cut-off date of 11 Aug 2017. The pooled data set comprised a total of 23 subjects with TFL (16 from Cohort 2 and 7 from Cohort 3) and 14 subjects with PMBCL (8 subjects from Cohort 2 and 6 subjects from Cohort 3) who had received axicabtagene ciloleucel. The ORR based on the investigator´s assessment was comparable between DLBCL (83%) and the sum of TFL/PMBCL (76%). Some variability was seen with 87% (95% CI: 66%, 97%) for TFL and at 57% (95% CI: 29%, 82%) for PMBCL however better outcomes in terms of time-dependent endpoints. Given the small sample size of these subgroups, there are no definite conclusions from these results.

Scholar-1

A retrospective, patient-level, pooled analysis of outcomes in refractory aggressive NHL (N = 636) was conducted (Crump et al., 2017).

Of 636 Scholar-1 evaluable patients, 389 patients are comprised from two randomized phase 3 clinical studies (170 patients in CORAL, 219 patients in LY12), while 247 patients (MAYO N=82, MDACC N=165) are gained from retrospective databases. Scholar-1 was developed as a companion study to ZUMA-1 to provide context for interpreting the ZUMA-1 results. The analysis included patients who had not responded (stable disease [SD] or PD) to their last line of therapy, or had relapsed within 12 months after ASCT. The ORR was 26% [95% CI (21, 31)] and CR rate was 7% [95% CI (3, 15)], with a median OS of 6.3 months. The historic ORR was pre-specified in ZUMA-1 phase 2 as 20%. This was in general acknowledged. However, after obtaining the historical control data of Scholar-1, the rate seems to be too low. The current point estimate of the Scholar-1 meta-analysis for the response rate was 25.7% (95% CI: 20.9%, 31.3%). In this light, further analyses are required to show that the ORR in ZUMA-1 is also ("significantly") higher than the refined historic control based on the point estimate. Furthermore, the uncertainty in the estimate should be taken into consideration by comparing the results of ZUMA-1 also to the upper limit of the confidence interval.

A re-analysis as "worst case" scenario was performed, by excluding patients with ECOG 2-4, patients with unknown ECOG, and patient's whose baseline assessment was more than 3 months before relapse / refractory disease was diagnosed. With these patients, a head to head comparison of response (CR+PR), CR and OS comparing SCHOLAR-1 and ZUMA-1 was conducted. In this comparison, the difference in response rates between SCHOLAR-1 ("worst case" subset) and ZUMA-1 (mITT set) was 53.1% (43.6%, 62.5%), the difference in CR rates was 46.9% (36.4%, 57.4%), and the hazard ratio for the reduction in the risk of death for subjects in the ZUMA-1 study was 0.4 (0.29, 0.56). Using the ITT set and central review, the difference for ORR between Scholar-1 (30.1%) and ZUMA-1 phase 2 (66%) was 35.9% and for CR between Scholar-1 (11.5%) and ZUMA-1 phase 2 (47%) 35.5%. These values are lower than these provided by the applicant, but however indicate a superior treatment effect for Yescarta.

Comparison of patients' covariates of ZUMA-1 and Scholar-1 limited to only CORAL and LY12 shows a rather equal distribution of patients with regard to gender, IPI-score, and proportion of patients with relapse after ASCT. The proportion of patients with DLBCL was higher in Scholar-1 (90% vs. 76%). ZUMA-1 even has a larger proportion of patients with worse disease stages and higher numbers of already received chemotherapy numbers. While ZUMA-1 only included patients with ECOG-scores of 0-1, this applies to only 86% of Scholar-1 patients. The provided sensitivity analysis of the standardized estimates and comparisons of response by ECOG category (applicant´s answer on LOQ 172) showed –as expected– that patients with ECOG-0 and 1 had better outcomes as patients with ECOG 2-4. In detail, table 9 shows that e.g. with respect to the group of patients being refractory to second-or-greater-lines-of therapy, 24 % of these had ECOG 0/1, while 8% had ECOG 2-4. The same applies for patients, who had a relapse after ASCT: While 8% of the responder had ECOG 0/1, only 1% had ECOG 2-4.

It is acknowledged, that DLBCL, PMBLC and TFL all are classified as large cell lymphoma due to their similarities with respect to pathogenesis, treatment and outcome. PMBCL and transformed FL are typically treated along a DLBCL treatment paradigm. In accordance with the updated WHO classification (Swerdlow 2016) transformed FL is not recognized as an entity but as DLBCL – which is nevertheless an heterogenous group- therefore it was considered redundant to be specifically mentioned in the indication. The indication has further been revised (see SmPC section 4.1) reflecting the most recent revision of the WHO classification (revised 4th edition 2017) of B-cell lymphoma subtypes, as: YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy.

A detailed description of the patients based on genetic analyses and histology according to the WHO 2016 classification is included within section 5.1 of the SmPC, while referring to the limited relevance of the genetics and to the issues of the retrospective analysis. Data on genetics will be collected prospectively as part of post-authorization studies (see RMP).

Currently, several ZUMA studies are ongoing or planned. Updated efficacy data from the ongoing ZUMA-1 study (Cohorts 1 & 2) would become available by 4Q 2018. The durability of the ongoing responses and additional survival data at 24 months would be provided (see RMP).

The applicant provided interim data after treatment of 34/ 50 patients within cohort 3. While these data are not part of the MAA, they may support the ZUMA-1 phase 2 data, particularly those of TFL (n=7) and PMBCL (n=6). While the median follow-up time 5.9 months (range: 1.0 to 9.5 months), the efficacy data are consistent to those of ZUMA-1 phase 2 with respect to ORR sec(62%) and a CR rate of 44% at the data cutoff date of 11 Aug 2017. The list of planned studies provided by the Applicant also contains ZUMA-7, with the indication is limited to second line DLBCL patients and with randomized open-label design to demonstrate superiority to SOC in terms of EFS. ZUMA-7 trial is expected to provide further information as evaluation of the treatment on patient reported outcomes (PROs) and quality of life (QoL) compared to SOC is part of the secondary study objectives (see RMP).

2.4.9. Conclusions on the clinical efficacy

Overall, a clinically relevant efficacy of the treatment with YESCARTA in Zuma -1 trial in patients with DLBCL and patients with PMBCL with significant duration has been demonstrated.

The CHMP endorsed the CAT conclusion on clinical efficacy as described above.

2.5. Clinical safety

A total of 136 subjects were enrolled into ZUMA-1 and ZUMA-2 combined (120 subjects in ZUMA-1 and 16 subjects in ZUMA-2). 119 of 136 (88%) subjects were treated with axicabtagene ciloleucel or KTE-C19 (XLP). All treated subjects completed axicabtagene ciloleucel infusion. The integrated dataset comprises 119 subjects: In ZUMA 1, no bridging therapy was permitted between the time of leukapheresis and infusion of axicabtagene ciloleucel. Within ZUMA-1 another cohort (so-called cohort 3) was recruited that received prophylactic treatment with tocilizumab once and levetiracetam daily in an attempt to reduce the incidence of CRS and neurological AE. This cohort comprised 39 patients in total, 34 of which were included in the safety analysis as they had received axicabtagene ciloleucel, these patients were reported in the most recent update.

Since patients within ZUMA-2 were treated with product that was manufactured using a different process and patients within cohort 3 of ZUMA-1 received prophylactic tocilizumab and levetiracetam the updated safety analysis included only patients from ZUMA-1 phase 1 and phase 2, altogether 108 patients. Supportive data summaries are provided for a subset of 13 subjects with relapsed/refractory aggressive B-cell NHL (diffuse large B-cell lymphoma [DLBCL], primary mediastinal B-cell lymphoma [PMBCL] and transformed follicular lymphoma [TFL]) treated in NCI Study 09-C-0082. Additional preliminary safety data are summarized separately for 11 adult subjects and 4 paediatric subjects with B precursor ALL treated in ZUMA-3 and ZUMA-

4, respectively. Data from ZUMA-3 and ZUMA-4 are not integrated with data from the lymphoma studies or with each other, principally because the patient populations—adult and pediatric B lineage ALL—have different clinical features, treatment, and disease courses. ZUMA-2, ZUMA-3 and ZUMA-4 are ongoing and the data should be regarded as preliminary.

Patient exposure

Table 25: patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term safety data
Open studies (Main)	136	123	116	?
Open studies (Supportive)	30	28	21	?

ZUMA-1 & 2

Exposure summaries to both conditioning chemotherapy and treatment are given in Table 26 and Table 27 respectively. Among all 119 treated subjects, 116 subject (97%) received within 10% of the planned dose of 2 x 10^6 anti-CD19 CAR T cells/kg (or a 2 x 10^8 anti-CD19 CAR T cells for subjects weighing > 100 kg).

Table 26: Exposure to Conditioning Chemotherapy – ZUMA-1 and ZUMA-2

	ZUMA-1 (N = 108)	ZUMA-2 (N = 11)	Overall (N = 119)
Total BSA adjusted cumulative dose cyclophosphamide (mg/m^2)			
N	108	11	119
Mean (STD)	1502.1 (42.0)	1500.0 (0.0)	1501.9 (40.0)
Median	1500.0	1500.0	1500.0
Min, Max	(1329.0, 1900.0)[1]	(1500.0, 1500.0)	(1329.0, 1900.0)[1]
Subjects receiving intended cumulative dose[2] (n [%])	106 (98)	11 (100)	117 (98)
Total BSA adjusted cumulative dose fludarabine (mg/m^2)			
N	108	11	119
Mean (STD)	89.9 (0.9)	90.0 (0.0)	89.9 (0.8)
Median	90.0	90.0	90.0
Min, Max	(81.0, 90.0)	(90.0, 90.0)	(81.0, 90.0)
Subjects receiving intended cumulative dose[1] (n [%])	108 (100)	11 (100)	119 (100)

Abbreviations: BSA, body surface area; max, maximum; min, minimum; STD, standard deviation.

Notes: Percentages were calculated using the number of subjects treated as the denominator.

[1] The maximal dose shown was incorrect in the CSS/ISS dataset; the value has been corrected to 1500 mg/m^2 in the primary analysis of the ZUMA-1 clinical study (Module 5.3.5.1, KTE-C19-101, Clinical Study Report).

[2] Subjects receiving ± 10% of the intended dose are included. The total intended cumulative dose of cyclophosphamide is 1500 mg/kg, and the total intended cumulative dose of fludarabine is 90 mg/m^2.

Table 27: Exposure to Axicabtagene Ciloleucel or KTE-C19 (XLP) – ZUMA-1 and ZUMA-2

	ZUMA-1 (N = 108)	ZUMA-2 (N = 11)	Overall (N = 119)
KTE-C19 dose[1] (× 10^6 anti-CD19 CAR T cells/kg)			
N	108	11	119
Mean (STD)	1.9 (0.2)	2.0 (0.0)	1.9 (0.2)
Median	2.0	2.0	2.0
Min, Max	(1.1, 2.2)	(1.9, 2.0)	(1.1, 2.2)
Subjects receiving ± 10% planned dose[2] (n [%])	105 (97)	11 (100)	116 (97)
Transduction rate (%)			
N	108	11	119
Mean (STD)	51.7 (15.0)	52.8 (14.7)	51.8 (14.9)
Median	52.3	51.1	52.1
Min, Max	(10.9, 85.1)	(33.1, 76.7)	(10.9, 85.1)
Total number of anti-CD19 CAR T cells (× 10^6)			
N	108	11	119
Mean (STD)	159.0 (33.6)	170.0 (18.4)	160.0 (32.6)
Median	162.0	160.0	160.0
Min, Max	(63.6, 200.0)	(150.0, 200.0)	(63.6, 200.0)
Total number of T cells infused (× 10^6)			
N	108	11	119
Mean (STD)	337.4 (132.4)	342.7 (85.2)	337.9 (128.5)
Median	301.1	364.7	302.1
Min, Max	(149.1, 892.9)	(197.1, 453.2)	(149.1, 892.9)

Abbreviations: CAR, chimeric antigen receptor; max, maximum; min, minimum; STD, standard deviation.
Note: Percentages were calculated using the number of subjects treated as the denominator.
[1] Both axicabtagene ciloleucel and KTE-C19 (XLP) comprise anti-CD19 CAR T cells; the products differ in their manufacturing processes, as described in Section 2.1 and Section 2.2. In ZUMA-2, of the 11 subjects treated as of the data cutoff date, the first 9 subjects were treated with axicabtagene ciloleucel and the last 2 subjects were treated with KTE-C19 (XLP).
[2] The calculation was based on a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg or a flat dose of 2 x 10^8 anti-CD19 CAR T cells.

ZUMA-3 & 4

Exposure summaries to both conditioning chemotherapy and treatment are given in Table 28 and Table 27 respectively. In both studies all subjects received the intended cumulative conditioning doses.

Note that for ZUMA-3, subjects could have received a target dose of 1 × 10^6 or 2 x 10^6 cells/kg, and the actual doses were 1 × 10^6 cells/kg for 5 subjects; 1.3 × 10^6 cells/kg for 1 subject; and 2 × 10^6 cells/kg for 5 subjects. All subjects in both studies received within 10% of the planned dose of 1 or 2 x 10^6 anti-CD19 CAR T cells/kg.

Table 28: Exposure to Conditioning Chemotherapy – ZUMA-3 and ZUMA-4

Exposure Parameter	ZUMA-3 (N = 11)	ZUMA-4 (N = 4)
Total BSA-adjusted cumulative dose, cyclophosphamide (mg/m^2)		
N	11	4
Mean (STD)	900.0 (0.0)	900.0 (0.0)
Median	900.0	900.0
Min, Max	(900.0, 900.0)	(900.0, 900.0)
Subjects receiving intended cumulative dose[1] (n [%])	11 (100)	4 (100)
Total BSA-adjusted cumulative dose, fludarabine (mg/m^2)		
N	11	4
Mean (STD)	75.0 (0.0)	75.0 (0.0)
Median	75.0	75.0
Min, Max	(75.0, 75.0)	(75.0, 75.0)
Subjects receiving intended cumulative dose[1] (n [%])	11 (100)	4 (100)

Abbreviations: BSA, body surface area; max, maximum; min, minimum; STD, standard deviation.
Note: ZUMA-3 and ZUMA-4 data are preliminary and have not been fully verified against source documents.
[1] Subjects receiving ± 10% of the intended dose are included. The total cumulative dose of cyclophosphamide is 900 mg/m^2, and the total intended cumulative dose of fludarabine is 75 mg/m^2.

Table 29: Exposure to KTE-C19 (XLP) – ZUMA-3 and ZUMA-4

	ZUMA-3 (N = 11)	ZUMA-4 (N = 4)
KTE-C19 dose (× 10^6 anti-CD19 CAR T cells/kg)		
N	11	4
Mean (STD)	1.5 (0.5)	2.1 (0.1)
Median	1.3	2.1
Min, Max	(1.0, 2.0)	(2.0, 2.1)
Subjects receiving ± 10% planned dose[2] (n [%])	11 (100)[1]	4 (100)
Transduction rate (%)		
n	11	4
Mean (STD)	56.8 (11.8)	49.3 (15.0)
Median	53.2	49.9
Min, Max	(38.4, 77.6)	(31.1, 66.5)
Total number of anti-CD19 CAR T cells (× 10^6)		
n	11	4
Mean (STD)	123.6 (46.5)	100.3 (48.7)
Median	130.0	90.5
Min, Max	(56.0, 200.0)	(60.0, 160.0)
Total number of T cells infused (× 10^6)		
n	11	4
Mean (STD)	224.9 (92.8)	239.8 (190.8)
Median	221.8	176.5
Min, Max	(105.7, 376.6)	(91.7, 514.5)

Abbreviations: CAR, chimeric antigen receptor; max, maximum; min, minimum; STD, standard deviation. All subjects in ZUMA-3 and ZUMA-4 received KTE-C19 (XLP), which is manufactured by a modified processes compared with that of axicabtagene ciloleucel, as described in Section 2.1and Section 2.2.

Note: ZUMA-3 and ZUMA-4 data are preliminary and have not been fully verified against source documents. Note: ZUMA-3 and ZUMA-4 data are preliminary.

[1] Actual adjusted doses of anti-CD19 CAR T cells were 1 × 10^6 cells/kg for 5 subjects; 1.3 × 10^6 cells/kg for 1 subject; and 2 × 10^6 cells/kg for 5 subjects.

[2] The calculation was based on target doses of or 2 x 10^6 anti-CD19 CAR T cells/kg in ZUMA-3 and 2 x 10^6 anti-CD19 CAR T cells/kg in ZUMA-3

NCI 09-C-0082 Subset

Exposure summaries to both conditioning chemotherapy and treatment are given in Table 30 and Table 31 respectively. Note that all subjects received fludarabine on the same days as cyclophosphamide.

Table 30: Exposure to Conditioning Chemotherapy – NCI 09-C-0082 Subset

Exposure Parameter	NCI 09-C-0082 (N = 13)
Cyclophosphamide (n [%])	
300 mg/m^2 × 3 days	11 (84.6)
500 mg/m^2 × 3 days	2 (15.4)
Fludarabine (n [%])	
30 mg/m2 × 3 days	13 (100.0)

Table 31: Exposure to Anti-CD19 CAR T Cells – NCI 09-C-0082 Subset

Exposure Parameter	NCI 09-C-0082 (N = 13)
Anti-CAR T cell dose (× 10^6 CAR T cells/kg)	
N	13
Mean (STD)	2.3 (1.10)
Median	2.0
Min, Max	2.0, 6.0
Transduction rate (%)	
N	13
Mean (STD)	48.0 (15.24)
Median	46.0
Min, Max	26.0, 75.0
Total number of CAR T cells (× 10^6)	
N	13
Mean (STD)	214.1 (112.38)
Median	177.5
Min, Max	130.7, 572.0
Total T cells infused (× 10^6)	
N	13
Mean (STD)	530.7 (512.40)
Median	377.6
Min, Max	209.6, 2200.0

Abbreviations: CAR, chimeric antigen receptor; max, maximum; min, minimum; STD, standard deviation.
Note: Subjects in NCI 09-C-0082 received cryopreserved anti-CD19 CAR T cells produced by the NCI. The products are produced using the same anti-CD19 CAR construct, the same retroviral vector, and the same retrovirus producer clone and have been shown to have similar in-process parameters as axicabtagene ciloleucel, as described in Section 2.1.

Adverse events

All AEs occurring after the start of conditioning chemotherapy were considered to be treatment-emergent and will be referred to as AEs throughout the text, whereas those associated with leukapheresis were defined in 2 ways: 1) events that were deemed related to leukapheresis by the investigator, and 2) events that occurred on the day of or the day after leukapheresis. AEs were considered if they occurred within 30 days after cell infusion, though for selected categories (CRS, neurologic events, infections, and cytopenias), AEs with onset after Day 30 were also examined.

Table 32 Adverse Events

	Phase 1 (N = 7)	Phase 2 (N = 101)	Overall (N = 108)
Any TEAE	7 (100)	101 (100)	108 (100)
Any TE Neurologic event	6 (86)	65 (64)	71 (66)
Worst Grade 5	0 (0)	0 (0)	0 (0)
due to disease progression	0 (0)	0 (0)	0 (0)
Worst Grade >= 3	4 (57)	29 (29)	33 (31)
Any Serious TE Neurologic event	1 (14)	26 (26)	27 (25)
Worst Grade 5	0 (0)	0 (0)	0 (0)
due to disease progression	0 (0)	0 (0)	0 (0)
Worst Grade >= 3	1 (14)	23 (23)	24 (22)
Any TE CRS	6 (86)	94 (93)	100 (93)
Worst Grade 5	0 (0)	1 (1)	1 (1)
due to disease progression	0 (0)	0 (0)	0 (0)
Worst Grade >= 3	1 (14)	12 (12)	13 (12)

Adverse events are coded using MedDRA version 19.0 and graded per CTCAE 4.03.

Table 33 AEs of Any Severity Occurring in ≥ 10% of Subjects in Phase 1 and Phase 2 Combined, by Preferred Term (Safety Analysis Set; N = 108)

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with Any TE Adverse Event	108 (100)	0 (0)	3 (3)	27 (25)	70 (65)	8 (7)
Pyrexia	94 (87)	17 (16)	62 (57)	15 (14)	0 (0)	0 (0)
Anaemia	72 (67)	3 (3)	20 (19)	46 (43)	3 (3)	0 (0)
Hypotension	63 (58)	19 (18)	29 (27)	14 (13)	1 (1)	0 (0)
Nausea	63 (58)	42 (39)	21 (19)	0 (0)	0 (0)	0 (0)
Fatigue	57 (53)	32 (30)	22 (20)	3 (3)	0 (0)	0 (0)
Decreased appetite	55 (51)	37 (34)	16 (15)	2 (2)	0 (0)	0 (0)
Headache	50 (46)	40 (37)	9 (8)	1 (1)	0 (0)	0 (0)
Neutropenia	49 (45)	1 (1)	5 (5)	10 (9)	33 (31)	0 (0)
Diarrhoea	48 (44)	33 (31)	10 (9)	5 (5)	0 (0)	0 (0)
Hypoalbuminaemia	43 (40)	17 (16)	25 (23)	1 (1)	0 (0)	0 (0)
Hypocalcaemia	43 (40)	20 (19)	16 (15)	7 (6)	0 (0)	0 (0)
Tachycardia	43 (40)	38 (35)	3 (3)	2 (2)	0 (0)	0 (0)
Chills	40 (37)	33 (31)	7 (6)	0 (0)	0 (0)	0 (0)
Encephalopathy	40 (37)	11 (10)	5 (5)	22 (20)	2 (2)	0 (0)
Febrile neutropenia	38 (35)	0 (0)	4 (4)	32 (30)	2 (2)	0 (0)
Hyponatraemia	38 (35)	25 (23)	1 (1)	12 (11)	0 (0)	0 (0)
Thrombocytopenia	38 (35)	6 (6)	6 (6)	11 (10)	15 (14)	0 (0)
Vomiting	37 (34)	31 (29)	5 (5)	1 (1)	0 (0)	0 (0)
Hypokalaemia	35 (32)	25 (23)	7 (6)	3 (3)	0 (0)	0 (0)
Neutrophil count decreased	35 (32)	0 (0)	1 (1)	6 (6)	28 (26)	0 (0)
Hypoxia	34 (31)	1 (1)	21 (19)	11 (10)	1 (1)	0 (0)
Tremor	33 (31)	27 (25)	4 (4)	2 (2)	0 (0)	0 (0)
White blood cell count decreased	33 (31)	1 (1)	1 (1)	3 (3)	28 (26)	0 (0)
Constipation	32 (30)	25 (23)	7 (6)	0 (0)	0 (0)	0 (0)
Cough	31 (29)	25 (23)	6 (6)	0 (0)	0 (0)	0 (0)
Hypophosphataemia	31 (29)	6 (6)	5 (5)	18 (17)	2 (2)	0 (0)
Platelet count decreased	30 (28)	7 (6)	6 (6)	8 (7)	9 (8)	0 (0)
Confusional state	29 (27)	8 (7)	11 (10)	10 (9)	0 (0)	0 (0)
Dizziness	23 (21)	21 (19)	2 (2)	0 (0)	0 (0)	0 (0)
Dyspnoea	23 (21)	15 (14)	6 (6)	2 (2)	0 (0)	0 (0)
Lymphocyte count decreased	23 (21)	0 (0)	0 (0)	2 (2)	21 (19)	0 (0)
Alanine aminotransferase increased	22 (20)	11 (10)	5 (5)	5 (5)	1 (1)	0 (0)
Sinus tachycardia	22 (20)	17 (16)	5 (5)	0 (0)	0 (0)	0 (0)
Leukopenia	21 (19)	0 (0)	3 (3)	5 (5)	13 (12)	0 (0)
Oedema peripheral	21 (19)	15 (14)	6 (6)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	20 (19)	5 (5)	10 (9)	5 (5)	0 (0)	0 (0)
Hypomagnesaemia	20 (19)	19 (18)	1 (1)	0 (0)	0 (0)	0 (0)

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Aphasia	19 (18)	5 (5)	6 (6)	8 (7)	0 (0)	0 (0)
Aspartate aminotransferase increased	19 (18)	11 (10)	2 (2)	6 (6)	0 (0)	0 (0)
Somnolence	18 (17)	3 (3)	6 (6)	8 (7)	1 (1)	0 (0)
Hypertension	17 (16)	2 (2)	7 (6)	8 (7)	0 (0)	0 (0)
Muscular weakness	17 (16)	9 (8)	7 (6)	1 (1)	0 (0)	0 (0)
Pleural effusion	17 (16)	9 (8)	6 (6)	2 (2)	0 (0)	0 (0)
Weight decreased	17 (16)	7 (6)	10 (9)	0 (0)	0 (0)	0 (0)
Abdominal pain	16 (15)	10 (9)	4 (4)	2 (2)	0 (0)	0 (0)
Back pain	16 (15)	10 (9)	5 (5)	1 (1)	0 (0)	0 (0)
Myalgia	16 (15)	13 (12)	2 (2)	1 (1)	0 (0)	0 (0)
Hypogammaglobulinaemia	15 (14)	7 (6)	8 (7)	0 (0)	0 (0)	0 (0)
Anxiety	14 (13)	10 (9)	3 (3)	1 (1)	0 (0)	0 (0)
Dehydration	13 (12)	5 (5)	5 (5)	3 (3)	0 (0)	0 (0)
Dry mouth	13 (12)	13 (12)	0 (0)	0 (0)	0 (0)	0 (0)
Insomnia	13 (12)	8 (7)	5 (5)	0 (0)	0 (0)	0 (0)
Pain in extremity	13 (12)	8 (7)	5 (5)	0 (0)	0 (0)	0 (0)
Arthralgia	11 (10)	8 (7)	3 (3)	0 (0)	0 (0)	0 (0)

Note: Preferred terms are sorted in descending order of total frequency count.
Adverse events are coded using MedDRA Version 19.0 and graded per CTCAE 4.03.

Serious adverse event / deaths / other significant events

Serious adverse events

Table 34 SAEs in > 1 Subject – ZUMA-1 safety analysis set

MedDRA Preferred Term	Phase 1 and 2 Combined (N = 108) n (%)
Subjects with any Serious TE Adverse Event	59 (55)
Encephalopathy	19 (18)
Lung infection	8 (7)
Pyrexia	8 (7)
Pneumonia	6 (6)
Confusional state	5 (5)
Febrile neutropenia	5 (5)
Aphasia	4 (4)
Atrial fibrillation	4 (4)
B-cell lymphoma	4 (4)
Cardiac arrest	4 (4)
Urinary tract infection	4 (4)
Acute kidney injury	3 (3)
Agitation	3 (3)
Ejection fraction decreased	3 (3)
Hypotension	3 (3)
Hypoxia	3 (3)
Neutropenia	3 (3)
Somnolence	3 (3)
Atrial flutter	2 (2)
Delirium	2 (2)

Note: Preferred terms are sorted in descending order of total frequency count.
Adverse events are coded using MedDRA Version 19.0 and graded per CTCAE 4.03.
Percentages are calculated using N in each column as the denominator.

Deaths

Table 35 Deaths

		Phase 2		
	Phase 1 (N =7)	Cohort 1 (N =77)	Cohort 2 (N =24)	Total (N =101)
Subjects Who Died	4 (57)	38 (49)	6 (25)	44 (44)
Primary Cause of Death				
Adverse Event	1 (14)	1 (1)	2 (8)	3 (3)
Progressive Disease	3 (43)	35 (45)	2 (8)	37 (37)
Other[a]	0 (0)	2 (3)	2 (8)	4 (4)
Deaths that occurred <= 30 days of axicabtagene ciloleucel infusion	1 (14)	1 (1)	1 (4)	2 (2)
Deaths that occurred > 30 days through 3 months (92 days) of axicabtagene ciloleucel infusion	1 (14)	2 (3)	1 (4)	3 (3)
Deaths that occurred > 3 months (92 days) after axicabtagene ciloleucel infusion	2 (29)	35 (45)	4 (17)	39 (39)

a The 4 subjects with the cause of death noted as "Other" died after disease progression and after receiving subsequent cancer therapy.

Four patients died due to an AE. Two of these were considered related to axicabtagene ciloleucel. In one case the initiating event was a grade 4 CRS with cardiac arrest, the second case was a patient who developed haemophagocytic lymphohistiocytosis, a rare disorder that is characterised by activation and proliferation of macrophages and histiocytes that is primarily caused by a preceding event that leads to activation and proliferation of T cells. One case of fatal pulmonary embolism was considered unrelated to axicabtagene ciloleucel.

In the supportive dataset three additional deaths were observed, one CRS and two infections (clostridium and mucormycosis).

ZUMA-1 cohort 3

There were 11 deaths at time of cut-off, all but one due to disease progression. One subject died due to cerebral oedema 9 days after axicabtagene ciloleucel infusion. This subject had rapidly progressing disease and a complicated course prior to administration of axicabtagene ciloleucel. After administration he developed signs of CRS and was treated accordingly. On day 7 after administration he developed brain oedema and brain herniation. He died on day 8, the death was considered causally related to axicabtagene ciloleucel. Retrospective analyses indicated elevated cytokine levels compatible with an ongoing inflammatory process.

Safety Following Retreatment with Axicabtagene Ciloleucel in Phase 1 and Phase 2

Retreatment was done for 1 subject in Phase 1 and 9 subjects in Phase 2. The overview profile following retreatment in Phase 2 was consistent with that reported for the main analysis of Phase 2 data: all 9 subjects had AEs; 4 subjects had SAEs; 8 subjects had conditioning chemotherapy-related AEs, 6 of which were Grade 3 or higher; 9 subjects had axicabtagene ciloleucel-related AEs, 4 of which were Grade 3 or higher; 6 subjects had CRS (no Grade 3 or higher); and 5 had neurologic events, 2 of which were Grade 3 or higher. For Phase 1, a summary of AEs during retreatment was not provided because only 1 subject was retreated.

Adverse Events of special interest

Cytokine release syndrome

CRS occurred in 93% of patients, 12% of whom experienced Grade 3 or higher (severe, life threatening and fatal) CRS. The median time to onset was 2 days (range 1 to 12 days) and the median duration was 7 days, with a range of 2 to 29 days. Ninety-eight percent (98%) of patients recovered from CRS. The most common signs or symptoms associated with CRS include pyrexia (76%), hypotension (41%), hypoxia (21%), tachycardia (21%) and chills (19%). Serious adverse reactions that may be associated with CRS include acute kidney injury, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (SmPC, section 4.8).

The following algorithm for the management of CRS has been developed.

Table 36. CRS grading and management guidance

CRS Grade *(a)*	Tocilizumab	Steroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity *(b).*	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days. If not improving, manage as Grade 4 (below)
Grade 4 Life-threatening symptoms Requirements for ventilator support or continuous veno-venous haemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above. Consider alternate immunosuppressants if no improvement or if condition worsens.

N/A = not available/not applicable
(a) Lee et al 2014
(b) Refer to Table 2 for management of neurologic adverse reactions
(c) Refer to tocilizumab summary of product characteristics for details

Neurological adverse reactions

Neurologic adverse reactions occurred in 65% of patients, 31% of whom experienced Grade 3 or higher (severe or life threatening) adverse reactions. The median time to onset was 5 days (range 1 to 17 days). The median duration was 13 days, with a range of 1 to 191 days. Ninety-eight percent (98%) of all patients recovered from neurologic adverse reactions (SmPC, section 4.8).

The most common signs or symptoms associated with neurologic adverse reactions include encephalopathy (58%), tremor (31%), aphasia (18%) and delirium (17%). Serious adverse reactions including encephalopathy (20%), aphasia (4%), delirium (4%), and seizures (1%) have been reported in patients administered YESCARTA (SmPC, section 4.8).

Table 37: Neurologic Adverse Events Phase 1 and 2 Combined (Safety Analysis Set; N = 108)

Event n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Neurologic Event - Any	71 (66)	22 (20)	16 (15)	30 (28)	3 (3)	0 (0)
Encephalopathy	40 (37)	11 (10)	5 (5)	22 (20)	2 (2)	0 (0)
Tremor	33 (31)	27 (25)	4 (4)	2 (2)	0 (0)	0 (0)
Confusional state	29 (27)	8 (7)	11 (10)	10 (9)	0 (0)	0 (0)
Aphasia	19 (18)	5 (5)	6 (6)	8 (7)	0 (0)	0 (0)
Somnolence	18 (17)	3 (3)	6 (6)	8 (7)	1 (1)	0 (0)
Agitation	10 (9)	3 (3)	2 (2)	5 (5)	0 (0)	0 (0)
Memory impairment	8 (7)	6 (6)	1 (1)	1 (1)	0 (0)	0 (0)
Mental status changes	6 (6)	1 (1)	3 (3)	2 (2)	0 (0)	0 (0)
Dysarthria	5 (5)	2 (2)	1 (1)	2 (2)	0 (0)	0 (0)

Event n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Hallucination	5 (5)	3 (3)	2 (2)	0 (0)	0 (0)	0 (0)
Ataxia	4 (4)	1 (1)	2 (2)	1 (1)	0 (0)	0 (0)
Restlessness	4 (4)	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)
Seizure	4 (4)	0 (0)	3 (3)	0 (0)	1 (1)	0 (0)
Delirium	3 (3)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
Disturbance in attention	3 (3)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)
Lethargy	3 (3)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Speech disorder	3 (3)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)
Depressed level of consciousness	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Disorientation	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Dyscalculia	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Hyperaesthesia	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Myoclonus	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Amnesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Coordination abnormal	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Delusion	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Dyskinesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Head discomfort	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoaesthesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Leukoencephalopathy	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Loss of consciousness	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Muscle spasticity	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Paraesthesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Stupor	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)

Note: Preferred terms are sorted in descending order of total frequency count.

Association of cytokine levels with neurological events (ZUMA-1, Safety set)

The AUC of IL-15 and IL-6 were measured throughout the first 4 weeks after infusion of axicabtagene ciloleucel in subjects who developed Grade 3 or higher neurologic events compared with levels in subjects who had Grade 2 or lower events. Bonferroni-stepdown corrected P-values, using a prespecified group of serum analytes, for IL-15 and IL-6 with neurologic events were 0.0003 and < 0.0001, respectively. Similarly, AUC of IL-2Rα (P = 0.0829) and IL-10 (P = 0.0123) were also associated with Grade 3 or higher neurologic events as compared to subjects with Grade 2 or lower events. The association between peak levels of IL-15, IL-6, IL-2Rα, IL-10 and Grade 3 or higher neurologic events respectively, was also significant.

Peak and cumulative levels of IL-2 and ferritin were also associated with Grade 3 or higher neurologic events (P < 0.05 after multiplicity adjustment) and were not associated with CRS.

The following serum markers, by peak or AUC, were also associated with both Grade 3 or higher neurologic events and Grade 3 or higher CRS: the cytokines TNF-α and IFN-γ; the chemokines IP-10 and IL-8; the pro-inflammatory marker IL-1ra; the immune effector molecule granzyme B; and the angiogenic factor VCAM-1 (all P < 0.05 by Bonferroni-stepdown).

Management of neurological events

Table 38. Neurologic adverse reaction grading and management guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Cerebral oedema

The safety data base was reviewed for a broad range of CNS AEs as well as specific events of cerebral oedema (cerebral congestion, vasogenic cerebral oedema, brain oedema, and cerebral oedema management). Baseline brain MRI was required for ZUMA-1. In addition, brain MRI and head computed tomography (CT) reports obtained for subjects with Grade 2 or higher neurologic events were reviewed.

After the data cutoff for the primary analysis of ZUMA-1, confirmed neurologic events of cerebral oedema were observed in 2 subjects across the lymphoma ZUMA studies.

One fatal event occurred in the safety expansion cohort (Cohort 3) of ZUMA-1, which enrolled distinct subjects from those enrolled in the pivotal portion of study.

The other case occurred in a subject with MCL treated on ZUMA 2 and resolved to baseline neurologic status (using KTE-C19 manufactured using the XLP process – a different process to YESCARTA).

Tumour lysis syndrome

One subject (1%) treated with axicabtagene ciloleucel developed non-serious Grade 3 TLS in ZUMA-1. No subject developed an AE of TLS in ZUMA-2.

Febrile neutropenia and infections

Febrile neutropenia was observed in 35% of patients after YESCARTA infusion. Infections occurred in 38% of patients in ZUMA-1. Grade 3 or higher (severe, life threatening, or fatal) occurred in 25% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 19%, 8%, and 6% of patients, respectively. The most common site of infection was in the respiratory tract (SmPC, section 4.8).

Prolonged Cytopenias

Grade 3 or higher neutropenia (including febrile neutropenia), anaemia and thrombocytopenia occurred in 93%, 63% and 56% of patients respectively. Grade 3 or higher neutropenia, thrombocytopenia, and anaemia still present at Day 30 or beyond occurred in 31%, 27%, and 17% of patients respectively (SmPC, section 4.8).

Hypogammaglobulinaemia

In ZUMA-1, hypogammaglobulinaemia occurred in 17% of patients. See section 4.4 for management guidance(SmPC, section 4.8).

Immunogenicity

The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for anti FMC63 prior to being treated with YESCARTA. An impact of these antibodies on efficacy or safety was not discernible (SmPC, section 4.8).

Secondary malignancies

Two patients in ZUMA-1 developed myelodysplastic syndrome, both were considered not related to conditioning chemotherapy or axicabtagene ciloleucel.

Analysis of replication competent retrovirus (RCR)

By protocol there were samples taken for RCR on Day 0 prior to administration of T cells, harvested and measured at 3, 6 and 12 months. Follow-up will involve yearly sampling but measuring only if positive at the 12 month visit, or before. No RCR have been observed.

Laboratory findings

Table 39 Laboratory Value Increases by Toxicity – ZUMA-1 and ZUMA-2

	Overall (N = 119)	
Laboratory Test	**Any Shift from Baseline n (%)**	**Any Shift from Baseline to Grade ≥ 3 n (%)**
Potassium (mmol/L)	11 (9)	3 (3)
Calcium (mmol/L)	9 (8)	5 (4)
Magnesium (mmol/L)	7 (6)	7 (6)
Sodium (mmol/L)	14 (12)	2 (2)
ALT (U/L)	98 (82)	14 (12)
AST (U/L)	91 (76)	12 (10)
Bilirubin (µmol/L)	54 (45)	8 (7)
Creatinine (µmol/L)	23 (19)	7 (6)
Urate (mmol/L)	24 (20)	24 (20)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Note: Percentages were calculated using the number of subjects treated as the denominator.
Note: Shifts are to Grade 3 or 4. No Grade 5 laboratory abnormalities were reported.
Note: No subjects had increases in hemoglobin, neutrophils, or platelets.

Table 40 Laboratory Value Decreases by Toxicity – ZUMA-1 and ZUMA-2

	Overall (N = 119)	
Laboratory Test	**Any Shift from Baseline n (%)**	**Any Shift from Baseline to Grade ≥ 3 n (%)**
Hemoglobin (mmol/L)	119 (100)	76 (64)
Neutrophils (10/L)	117 (98)	110 (92)
Platelets (10/L)	117 (98)	69 (58)
Potassium (mmol/L)	82 (69)	12 (10)
Calcium (mmol/L)	114 (96)	13 (11)
Magnesium (mmol/L)	100 (84)	0
Sodium (mmol/L)	105 (88)	33 (28)

Note: Percentages were calculated using the total number of subjects treated as the denominator.
Note: Shifts are to Grade 3 or 4. No Grade 5 laboratory abnormalities were reported.
Note: No subjects had decreases in ALT, AST, bilirubin, creatinine, or urate.

Safety in special populations

The following analyses are based on a combined lymphoma set of ZUMA-1 and ZUMA-2

Age

Comparing AE incidence in two age categories only neurologic events appear to be more common in the population more than 65 years of age.

Summary of Adverse Events by Age Group Safety Analysis Set of ZUMA-1 (Phase 1 and Phase 2 Cohorts 1 & 2)

Event	Age <65 N=81	Age 65-74 N=23	Age 75-84 N=4
Total AEs - n(%)	81 (100)	23 (100)	4 (100)
Serious AEs - n(%)	46 (57)	9 (39)	0
Fatal AEs - n(%)	3 (4)	1 (4)	0
Hospitalization/prolong existing hospitalization - n(%)	29 (36)	7 (30)	0
Life-threatening - n(%)	12 (15)	2 (9)	0
Psychiatric disorders - n(%)	36 (44)	11 (48)	2 (50)
Nervous system disorders - n(%)	70 (86)	18 (78)	3 (75)
Accidents and injuries - n(%)	6 (7)	2 (9)	1 (25)
Cardiac disorders - n(%)	53 (65)	16 (70)	3 (75)
Vascular disorders - n(%)	51 (63)	17 (74)	2 (50)
Cerebrovascular disorders - n(%)	2 (2)	0	0
Infections and infestations - n(%)	32 (40)	8 (35)	1 (25)
Anticholinergic syndrome - n(%)	0	0	0
Quality of life decreased - n(%)	0	0	0
Incidence of any postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures - n(%)	23 (28)	7 (30)	2 (50)
Other AE appearing more frequently in older patients			
Pyrexia	68 (84)	23 (100)	3 (75)
Decreased appetite	32 (40)	12 (52)	2 (50)
Encephalopathy	27 (33)	11 (48)	1 (25)
Muscular weakness	8 (10)	8 (35)	0
Hypertension	10 (12)	5 (22)	1 (25)

ECOG

The incidence of Grade 3 or higher CRS was higher for subjects with baseline ECOG score of 1 versus those with a score of 0.

Sex

Women appear to be more prone to AE. They had a numerically higher incidences of SAE, neurological SAE, grade 3 or higher neurological events and grade 3 or higher infections.

AE by total T cell number

Subjects who received product with total T-cells number ≤ the population median had a higher incidence of Grade 3 or higher CRS than subjects who received product with total T cells number > population median (17.6% vs 8.0%). **AE by transduction rate**

Subjects who received product with a transduction rate higher than the median rate had a higher incidence of Grade 3 or higher AEs (50% vs 35%) and Grade 3 or higher axicabtagene ciloleucel-related AEs (50% vs 35%).

AEs by Total Anti-CD19 CAR T-cell Dose Percentiles

There is a pattern with increases of AE incidence from the lowest quartile to the second quartile; however, within the highest quartile the incidence appears to be decreasing again.

AEs by IFN- gamma in co-culture

The following categories of AEs were more frequent in subjects dosed with product potency > the population median than in subjects dosed with product potency ≤ the population median: Grade 3 or Axicabtagene ciloleucel; higher SAE (48% vs 37.3%); Grade 3 or higher axicabtagene ciloleucel-related AE (70.0% vs 56.9%); Grade 3 or higher axicabtagene ciloleucel-related SAE (48.0% vs 37.3%); neurologic event (36.0% vs 19.6%); and neurologic SAE (26.0% vs 15.7%).

Immunological events

The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three of 94 patients in ZUMA-1 tested positive at baseline for antibodies to the murine antibody FMC63 used for the development of the anti-CD19 part of the CAR construct. One of these had evidence of binding to the cellular expressed construct. Clinical course seemed not distinguishable in these three patients compared to patients that were negative for anti-FMC63.

Anti-bovine serum albumin was detected in 30% of patients at baseline in ZUMA-1. Fifteen subjects (15%) were antibody positive post-baseline with a negative or no result at baseline, with fluctuating levels and no evidence of immune allergic reactions.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to adverse events

This is not applicable as this therapy is only administered once. There were no discontinuations during administration.

Post marketing experience

Not available.

2.5.1. Discussion on clinical safety

The safety population set for the primary analysis was originally comprised of 119 subjects from the combined ZUMA-1 & 2, thus presented a population affected by relapsed/refractory DLBCL, PMBCL and MCL. This approach was modified to include only patients from ZUMA-1 which is acceptable as there are relevant differences in the population and the treatment of patients recruited to ZUMA-2. Therefore, data from 108 patients of the ZUMA-1 trial (7 patients in Phase 1 and 101 patients in Phase 2) are considered as principal source of safety information. The data cutoff date for the updated analysis was 11.08.2017, at which time all patients would be followed for 12 months from axicabtagene ciloleucel infusion.

Patients were treated with doses of CAR-T cells of 1.1-2.2 x 10^6 CAR T cells/kg body weight. Currently the importance of the actually administered dose is not clear as the CAR T cells will proliferate in vivo. Given the general knowledge of lymphocyte proliferation it seems unlikely that a twofold difference in infused cells would be clinically meaningful, but this is of course dependent on the proliferative capability of the cells. The majority of patients was male (70%), white (90%) and from the USA (99%).

Serious adverse reactions occurred in 55% of patients. The most common serious adverse reactions include encephalopathy (20%), unspecified pathogen infections (15%), bacterial infections (5%), viral infections (5%), pyrexia (5%), and febrile neutropenia (5%) (SmPC section 4.8).

Close to all patients experienced adverse events related to the investigative product with many (over 80%) having Grade 3 or higher events and more than half in all trials having investigative product related SAEs, and a pattern could be distinguished whereby in particular events of encephalopathy, pyrexia, (febrile) neutropenia, anaemia, hypotension and hypoxia tend to form a non-negligible burden on the subject in the form of Grade 3 or higher AES and SAEs and treatment related deaths.

The most common Grade 3 or higher adverse reactions include encephalopathy (30%), unspecified pathogen infection (19%), cytokine release syndrome (12%), bacterial infection (8%), aphasia (7%), viral infection (6%), delirium (6%), hypotension (6%) and hypertension (6%).

The most serious and frequently occurring adverse reactions are CRS (93%), encephalopathy (58%), and infections (38%). Grade 3 or higher neutropenia, thrombocytopenia, and anaemia still present at Day 30 or beyond occurred in 31%, 27% and 17% of patients respectively (SmPC, section 4.8).
Sequelae of conditioning chemotherapy such as anaemia, cytopenias, neutropenic fever, infection are an expected AE for the treatment regimen. Axicabtagene ciloleucel may contribute to these AE via secondary mechanisms such as sequestration of lymphocytes and platelets following cytokine release or via mechanisms involving the bone marrow function. Neutropenia, neutropenic fever and infections are very common, as is thrombocytopenia. There were two deaths reported in the supportive dataset that were caused by infection. One death was caused by an intracranial haemorrhage following thrombocytopenia that was assessed as chemotherapy related, an infection may have contributed to the fatal outcome.

Cytokine release syndrome is very commonly observed and is clearly caused by axicabtagene ciloleucel. CRS occurred in 93% of patients, 12% of whom experienced Grade 3 or higher (severe, life threatening and fatal)

CRS. The median time to onset was 2 days (range 1 to 12 days) and the median duration was 7 days, with a range of 2 to 29 days. Ninety-eight percent (98%) of patients recovered from CRS (SmPC, section 4.8). CRS have been categorized as identified risk (see Risk Management Plan).

Cardiac failure has been observed as well as cardiac arrhythmia, possibly aggravated by serum electrolyte disturbances. CRS was the likely cause of one fatal case of haemophagocytic lymphohistiocytosis and one fatal case of brain injury following cardiac arrest.

The most common signs or symptoms associated with CRS include pyrexia (76%), hypotension (41%), hypoxia (21%), tachycardia (21%) and chills (19%). Serious adverse reactions that may be associated with CRS include acute kidney injury, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (SmPC, section 4.8).

The phenotypically similar tumour lysis syndrome appears to be less common as could be deduced from the low incidence of reported AE of acute kidney injury, hyperkalemia, hyperphosphataemia and increase in serum uric acid. However, a relevant shift to increased values of uric acid and creatinine is reported in the laboratory section which could point to a relevant frequency of tumour lysis syndrome that is not identified as such because of the predominant features of CRS. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to YESCARTA infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines (SmPC section 4.4).

Neurological adverse reactions, especially encephalopathy of varying degrees with symptoms and signs such as somnolence, confusion, tremor, headache or aphasia was observed in the majority of patients. 31% of subjects had a ≥ grade 3 neurological adverse reaction. The median time to the onset of neurological adverse reaction was 5 days (range 1-17) and the median time to resolution was 17 days. The relationship of CRS and the neurological adverse reaction still requires further clarification. A pathophysiological explanation of the observed encephalopathy seems rather obscure at present. Similar neurotoxicity has been observed with other forms of CD19 directed immunotherapies such as blinatumomab so there is a reason to believe that this is caused either by the intended pharmacological effect, i.e. cyotoxicity and cytokine release by CAR T cells to their natural CD19 positive target (B cells), CD19 expression on other cells of the central nervous system or crossreactivity to a yet unknown target. However, it may also be caused by systemic CRS in a population that is prone to this neurological AE. Serious neurologic adverse reactions including cerebral oedema have been been categorized as identified risk (see Risk Management Plan). Patients with a history of CNS disorders such as seizures or cerebrovascular ischemia may be at increased risk. Fatal and serious cases of cerebral oedema have been reported in patients treated with YESCARTA. Patients should be monitored for signs and symptoms of neurologic adverse reactions (Table 2). Patients should be monitored at least daily for 10 days at the qualified healthcare facility following infusion for signs and symptoms of neurologic toxicity. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Counsel patients to remain within proximity, of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Non-sedating, anti-seizure medicines should be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on YESCARTA. This includes the use of tocilizumab

(if concurrent CRS) and/or corticosteroids for moderate, severe or life threatening neurologic adverse reactions (SmPC section 4.4)

Serious infections have been very commonly observed with Yescarta. Patients should be monitored for signs and symptoms of infection before, during, and after Yescarta infusion and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines (SmPC, section 4.4). Infections have been categorized as identified risk (see Risk Management Plan).

Febrile neutropenia has been observed in patients after Yescarta infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated (SmPC, section 4.4).

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Screening for HBV, HCV, and HIV should be performed in accordance with clinical guidelines before collection of cells for manufacturing (SmPC, section 4.4).

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Yescarta. Hypogammaglobulinaemia has been very commonly observed in patients treated with Yescarta. Immunoglobulin levels should be monitored after treatment with Yescarta and managed using infection precautions, antibiotic prophylaxis and immunoglobulin replacement (SmPC, section 4.4). Hypogammaglobulinemia has been categorized as identified risk (see Risk Management Plan).

Allergic reactions may occur with the infusion of Yescarta. Serious hypersensitivity reactions including anaphylaxis, may be due to DMSO or residual gentamicin in Yescarta (SmPC, section 4.4).

Patients treated with Yescarta may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be conctacted to obtain instructions on patient samples to collect for testing (SmPC, section 4.4). Secondary malignancy has been categorized as potential risk (see Risk Management Plan).

Grade 3 or higher neutropenia (including febrile neutropenia), anaemia and thrombocytopenia occurred in 93%, 63% and 56% of patients respectively. Grade 3 or higher neutropenia, thrombocytopenia, and anaemia still present at Day 30 or beyond occurred in 31%, 27%, and 17% of patients respectively (SmPC, section 4.8). Cytopenias including aplastic anaemia have been categorized as potential risk (see Risk Management Plan).

The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for anti FMC63 prior to being treated with YESCARTA. An impact of these antibodies on efficacy or safety was not discernible. Immunogenicity has been categorized as potential risk (see Risk Management Plan).

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Yescarta infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines (SmPC, section 4.4). TLS has been categorized as potential risk (see Risk Management Plan).

There is limited experience with Yescarta in patients exposed to prior CD19-directed therapy. Yescarta is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy (SmPC, section 4.4).

There is a theoretical risk of aggravation of GvHD in patients who have previously undergone an allogeneic stem-cell transplant (allo-HSCT) and then received donor derived engineered CAR T cells (from prior allo-HSCT donor) for their relapsed non-Hodgkin lymphoma (NHL). No patients in the ZUMA-1 had previously undergone allo-HSCT.. Aggravation of GvHD has been categorized as potential risk (see Risk Management Plan).

Needle stick injuries may occur among health care providers, although they have been reduced by minimizing handling of body fluids and needles. No health care providers experienced exposure to axicabtagene ciloleucel during the ZUMA-1 study. Administration of axicabtagene ciloleucel is not associated with a risk of splash or spill and disposal of used and exposed materials should follow local biosafety guidelines. Transmission of infectious agents via product has been categorized as potential risk (see Risk Management Plan).

Axicabtagene ciloleucel must be prepared and administered per specifications or there is a potential risk of decrease in viability of the product. There have been no reports linked to decrease in viability of the product due to inappropriate preparation of cell infusion in the ZUMA 1 studies. Decrease in viability of the product due to inappropriate preparation of infusion has been categorized as potential risk (see Risk Management Plan).

The γ retroviral vector PG13-CD19-H3 Vector used for transduction of subject-derived autologous T cells is replication-defective and to date, no RCR has been detected in Vector lots or in axicabtagene ciloleucel final product lots. The risk of RCR occurring in subjects treated with axicabtagene ciloleucel is considered to be low due to 1) the vector and packaging cell line used, and 2) rigorous testing prior to release of the final product. Replication-competent retrovirus has been categorized as potential risk (see Risk Management Plan).

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult (SmPC, section 4.4).

Yescarta has moderate influence on the ability to drive and use machines. Due to the potential for neurologic events, including altered mental status or seizures, patients should refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions (SmPC, section 4.7).

There are no data regarding the signs of overdose with Yescarta (SmPC, section 4.9).

Missing information in several patient groups: Use in pregnancy and lactation, use in non-Caucasian patient populations, use in HIV, HCV positive patients, new occurrence or exacerbation of an autoimmune disorder and long term safety. Routine risk minimization activities recommend specific clinical measures to address these (see Risk Management Plan).

In an analysis of safety in several subgroups there was an increase of neurological events in subject ≥65 years and a higher incidence of SAE and ≥ grade 3 AE in women. The observed acute AE/ADR are to a large extent of limited duration and reversible. For the treatment of treatment-related AE the protocol ZUMA-1 was amended several times. In ZUMA-1 43/101 subjects were treated with tocilizumab (CRS 17, neurological events 33, other 5) and 27/101 subjects received glucocorticoids (CRS 6, neurological events 15, other 17). 25/101 received tocilizumab and glucocorticoids. No patient tested positive for replication-competent retrovirus so far. Testing will include a 12 months time-point, after this time-point testing will only be performed if a positive result has been obtained earlier or on clinical suspicion.

The updated safety analysis set confirms the initially performed analyses and there are no relevant new findings. Supportive data are available from 13 patients using different AE collection methodology and 15 patients in a different indication (B-precursor ALL). The safety database is therefore considered rather limited. The follow-up of patients is short, the median FU time in lymphoma dataset is 5.9 months, maximum 17.9 months. Safety data from a currently recruiting cohort (phase 3) will be provided (see RMP).

Safety data in the post marketing setting will be provided from a non-interventional post-authorisation safety study (PASS) based on a registry.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.2. Conclusions on the clinical safety

Axicabtagene ciloleucel treatment is associated with a high incidence of ADR of a severity of ≥ grade 3 and/or serious. Cytokine release syndrome and neurological adverse reactions are likely caused by axicabtagene ciloleucel while cytopenias are more likely to be predominantly related to conditioning chemotherapy or previous therapies.

The CAT considers the following measures necessary to address issues related to safety:

- A non-interventional post-authorisation safety study (PASS) based on a registry to assess the safety profile in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting.

The CHMP endorsed the CAT conclusion on clinical safety as described above.

2.6. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	Serious neurologic adverse reactions including cerebral oedema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia
Important potential risks	Secondary malignancy Immunogenicity

Summary of Safety Concerns	
	RCR TLS Aggravation of GvHD Transmission of infectious agents via product Decrease in viability of the product due to inappropriate preparation of infusion
Missing information	Use in pregnancy and lactation Use in non-Caucasian patient populations New occurrence or exacerbation of an autoimmune disorder 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				
Planned Non-Interventional Registry Study (PASS) Planned	Additional characterization of the identified risks, further evaluation of potential risks and missing information.	Identified risks, potential risks, and missing information	Protocol submission	Within 6 months of EC Decision
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				
Prescriber survey Planned	To assess the prescribers' understanding of the risks of YESCARTA	Serious neurologic adverse reactions including cerebral oedema CRS Decrease in viability of	Protocol submission	Within 6 months of EC Decision

Study/ Status	**Summary of objectives**	**Safety concerns addressed**	Milestones	**Due dates**
		the product due to inappropriate preparation of infusion		
ZUMA-1/ On-going	Phase 1/2 Study to assess safety and efficacy of axicabtagene ciloleucel in refractory aggressive NHL	Serious neurologic adverse reactions including cerebral oedema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Use in non-Caucasian patient populations Long term safety	Safety updates in PSUR Final report cohort 1 and 2:	Annual 28 Jul 2031
			Final report cohort 3	06 Oct 2032
ZUMA-2/ On-going	Phase 2 study to assess efficacy and safety of KTE-C19 in subjects with relapsed/refractory in Mantle Cell Lymphoma (MCL)	Serious neurologic adverse reactions including cerebral oedema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR	Safety updates in PSUR Final report	Annual 25 Sept 2032

Study/ Status	**Summary of objectives**	**Safety concerns addressed**	Milestones	**Due dates**
		TLS Use in non-Caucasian patient populations Long term safety		
ZUMA-3/ On-going	Phase 1/2 study to assess efficacy and safety of KTE-C19 in relapsed/refractory Adult ALL patients	Serious neurologic adverse reactions including cerebral oedema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Use in non-Caucasian patient populations Long term safety	Safety updates in PSUR Final report	Annual 12 Jul 2033
ZUMA-4/ On-going	Phase 1/2 study to assess efficacy and safety of KTE-C19 in relapsed/refractory pediatric ALL patients	Serious neurologic adverse reactions including cerebral oedema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR	Safety updates in PSUR Final report	Annual 23 Nov 2033

Study/ Status	**Summary of objectives**	**Safety concerns addressed**	Milestones	**Due dates**
		TLS Use in non-Caucasian patient populations Long term safety		
ZUMA-5/ On-going	Phase 2 multicenter study to assess efficacy and safety of axicabtagene ciloleucel in subjects with relapsed/refractory indolent NHL	Serious neurologic adverse reactions including cerebral oedema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Use in non-Caucasian patient populations Long term safety	Safety updates in PSUR Final report	Annual TBD
ZUMA-6/ On-going	Phase 1/2 supportive study to assess efficacy and safety of axicabtagene ciloleucel in combination with atezolizumab in refractory DLBCL patients	Serious neurologic adverse reactions including cerebral oedema CRS Cytopenias including aplastic anaemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR	Safety updates in PSUR Final report	Annual 30 Mar 2023

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		TLS Use in non-Caucasian patient populations Long term safety		

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious neurologic adverse reactions including cerebral oedema	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 PL sections 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: • HCP educational material • PAC • Controlled distribution program	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event Follow-up Questionnaire Additional pharmacovigilance activities: Registry, prescriber survey, and studies ZUMA-1 –ZUMA-6
CRS	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 PL sections 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: • HCP educational material • PAC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event Follow-up Questionnaire Additional pharmacovigilance activities: Registry, prescriber

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Interim supply chain strategy for tocilizumab • Controlled distribution program	survey, and studies ZUMA-1 –ZUMA-6
Cytopenias including aplastic anaemia	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry, and studies ZUMA-1 –ZUMA-6
Infections	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry, and studies ZUMA-1 –ZUMA-6
Hypogammaglobulinemia	Routine risk minimization measures: SmPC sections 4.4 and 4.8 PL section: 4 Use restricted to physicians experienced in the treatment of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional

Safety concern	Risk minimization measures	Pharmacovigilance activities
	hematological cancers Additional risk minimization measures: None	pharmacovigilance activities: Registry, and studies ZUMA-1 –ZUMA-6
Secondary malignancy	Routine risk minimization measures: SmPC sections 4.4 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry, and studies ZUMA-1 –ZUMA-6
Immunogenicity	Routine risk minimization measures: SmPC sections 4.8 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry, and studies ZUMA-1 –ZUMA-6

Safety concern	Risk minimization measures	Pharmacovigilance activities
RCR	Routine risk minimization measures: None Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry, and studies ZUMA-1 –ZUMA-6
TLS	Routine risk minimization measures: SmPC sections 4.4 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry, and studies ZUMA-1 –ZUMA-6
Aggravation of GvHD	Routine risk minimization measures: SmPC: section 4.4 PL: section 2 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures:None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry
Transmission of infectious agents via product	Routine risk minimization measures:	Routine pharmacovigilance

Safety concern	Risk minimization measures	Pharmacovigilance activities
	SmPC Sections 4.2 PL Section 3 Additional risk minimization measures: None	activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Decrease in viability of the product due to inappropriate preparation of infusion	Routine risk minimization measures: Awareness and adherence to the handling, preparation and administration guidelines Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in pregnancy and lactation	Routine risk minimization measures: SmPC sections 4.6 PL section 2 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry
Use in non-Caucasian patient population	Routine risk minimization measures: None Additional risk minimization	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	measures: None	Additional pharmacovigilance activities: Registry and studies ZUMA-1 –ZUMA-6
New occurrence or exacerbation of an autoimmune disorder	Routine risk minimization measures: SmPC section 5.1 Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry
Long term safety	Routine risk minimization measures: None Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry and studies ZUMA-1 –ZUMA-6

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.10.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

The applicant declared that axicabtagene ciloleucel has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers axicabtagene ciloleucel to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, YESCARTA (axicabtagene ciloleucel) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication of axicabtagene ciloleucel is: treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy.

3.1.2. Available therapies and unmet medical need

Patients with relapsed or refractory aggressive B-cell NHL are typically treated with rituximab and platinum-based chemotherapy regimens. The current standard of care for these patients is second-line chemotherapy plus autologous stem cell transplant (ASCT). However, only half of the patients with relapsed/refractory disease may undergo ASCT, as the others are ineligible for ASCT (due to an inadequate response to second line therapy, relapse after second or greater line of therapy, failure to mobilize stem cells, or presence of comorbidities). These patients have no curative options and thus have a clear unmet medical need.

3.1.3. Main clinical studies

The clinical package of Yescarta was primarily supported by data from ZUMA-1 phase 2 open-label, single-arm study which enrolled 111 adult patients with refractory or relapsed DLBCL patients –including DLBCL arising from follicular lymphoma and PMBCL.

3.2. Favourable effects

In ZUMA-1 phase 2, among 111 leukapherized subjects, 110 lots of axicabtagene ciloleucel were successfully manufactured (>99%) and 101 subjects (91%) received axicabtagene ciloleucel. The ORR based on the ITT-population and on the central review assessment was 66 % (95% CI: 56%, 75%) with a complete response rate of 47 %; based on the mITT-population and the investigator ORR was 83%. The estimated median DOR was 14.0 months (95% CI: 8.3, NE) and was not yet reached in patients who achieved CR with a median follow up of 15.1 months. The average remission rate of salvage therapy based on the SCHOLAR-1 results is about 25.7%. ORRs and 95% CIs for the Phase 2 Cohorts 1 and 2 combined were further analysed by baseline demographic and disease characteristics, product characteristics, and use of tocilizumab and systemic steroids. Mean ORRs for each subset ranged from 67% to 99% and were comparable to the ORR for the Phase 2 population overall (83%) based on the mITT and investigator´s assessment. No significant impact of subsets based on age, sex, disease type (DLBCL or PMBCL), and refractory subgroups, primary refractory status, refractory status to 2 or more consecutive lines of therapy, disease stage, IPI risk score, tumour burden, CD4:CD8 ratio of (> 1 or ≤ 1) and the use tocilizumab or steroids (yes or no) became appearant. Responses also were consistent in subjects whose tumours were retrospectively assessed as CD19+ (ORR = 85%) or CD19– (ORR = 75%).

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties about the favourable effects.

3.4. Unfavourable Effects

The most serious and frequently occurring adverse reactions are CRS (93%), encephalopathy (58%), and infections (38%). Most of the reported acute adverse events are likely to be a consequence of CRS such as pyrexia, chills, tachycardia, serum electrolyte changes, headache and myalgia are the consequences to the function of important organs such as hypoxia, hypotension, cardiac rhythm disturbances and acute kidney injury. Two of the reported deaths were likely a consequence of CRS. CRS occurs predominantly in the first two weeks after infusion and eventually subsides. Empirical treatment recommendations have been provided that take severity of CRS into account.

The availability of tocilizumab at all hospitals and associated centres must be ensured by the Marketing Authorisation Holder until an authorised treatment for CRS is available in the EU. Yescarta will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program. To mitigate the safety risks associated with the treatment of Yescarta, it must be ensured that hospitals and their associated centres that dispense Yescarta are specially qualified (see Annex II and RMP).

Neurological adverse reactions occurred in the majority of patients which appear to be mostly non-localising, i.e. encephalopathy with the symptoms and signs such as change in consciousness levels, disturbance of attention, somnolence, agitation, confusion and attention disturbance but there are also potentially localising symptoms and signs such as ataxia, dyskinesia, speech disorders and aphasia. A case of cerebral oedema with a fatal outcome has been reported from an expansion cohort of the ongoing clinical trial.

Grade 3 or higher neutropenia, thrombocytopenia, and anaemia still present at Day 30 or beyond occurred in 31%, 27% and 17% of patients respectively. Cytopenias were observed very commonly and involved all lineages (neutropenia, febrile neutropenia, anaemia thrombocytopenia and leukopenia) also associated with the occurrence of infections and bleeding. Infections were observed very commonly. There were two deaths reported in the supportive dataset that were caused by infection. One death was caused by an intracranial haemorrhage following thrombocytopenia that was assessed as chemotherapy related, an infection may have contributed to the fatal outcome.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is considered rather limited in terms of size and duration. The follow-up of patients is short, the median FU time in lymphoma dataset is 5.9 months, maximum 17.9 months. Safety data from a currently recruiting cohort (phase 3) will be provided (see RMP).

A PASS study using a registry is planned with the purpose of additional characterization of identified risks, further evaluation of potential risks and missing information with special focus on long-term safety to assess whether administration is associated with subsequent neoplasm (See RMP).

3.6. Effects Table

Table 41 Effects Table for axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma, after two or more lines of systemic therapy (data cut-off : 11 August 2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Complete response	CR per the revised International Working Group Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by study investigators	rate	all 111 enrolled patients (ITT-set): 55%	Historical control SCHOLAR-1: 7%		
Objective response rate	ORR defined as a CR or PR per the revised International Working Group Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by central review, ITT population	rate	ORR 66 % (95% CI: 56%, 75%)	Scholar-1 with a ORR of 25.7% (95%CI 20.9; 31.3)	Consistent effect in subgroups	
Duration of response	Median duration	months	Cohorts 1 and 2 combined 14 months.			
Unfavourable Effects						
Deaths/fatal AE			4%	NA		
Cytokine release syndrome	≥Grade 3		12%			
Tumour lysis syndrome	≥Grade 3		1%			
Neurological events	≥Grade 3		31%			
Infections	≥Grade 3		25%			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with axicabtagene ciloleucel at target doses of 2 x 10^6 anti-CD19 CAR T cells/kg body weight shows a significant increase of ORR and a clearly better efficacy profile compared to the retrospective global patient-level pooled study Scholar-1 and Coral in patients with aggressive forms of NHL, specifically DLBCL, PMBCL and transformed follicular lymphoma. The ORR of ZUMA-1 based on the ITT-population and central review lays about 66%, while the pre-specified ORR for SCHOLAR-1 was about 25.7%. The superiority of ORR in ZUMA-1 phase compared to SCHOLAR-1 is further supported by significant increase of DOR.

CRS and cytopenias are transient ADR that appear to be amenable to treatment. Neurological adverse reactions also appear to be transient, with only one case was judged as not resolved (mild memory impairment).

A PASS study using a registry is planned with the purpose of additional characterization of identified risks, further evaluation of potential risks and missing information with special focus on long-term safety to assess whether administration is associated with subsequent neoplasm.

3.7.2. Balance of benefits and risks

The treatment effect of Yescarta is considered clinically relevant. The safety profile of Yescarta is acceptable in view of the therapeutic context and the observed benefits.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of YESCARTA for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy is positive.

The CHMP endorsed the CAT conclusion on Benefit Risk balance as described above.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of YESCARTA is favourable in the following indication:

YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Key elements:

Availability of tocilizumab and site qualification

To minimise the risks associated with the treatment of YESCARTA, the MAH must ensure that hospitals and their associated centres that dispense YESCARTA are specially qualified in accordance with the agreed control distribution program.

The MAH must ensure on-site, immediate access to 4 doses of tocilizumab for each patient as CRS management medication prior to treating patients.

YESCARTA will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program.

The availability of tocilizumab at all hospitals and associated centres must be ensured by the MAH until an authorised treatment for CRS is available in the EU.

Educational program – Prior to the launch of YESCARTA in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where YESCARTA is marketed, all HCPs who are expected to prescribe, dispense, and administer YESCARTA shall be provided with a guidance document to:

- facilitate identification of CRS and serious neurologic adverse reactions
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that 4 doses of tocilizumab for each patient are available on site

Patient Educational program

To inform and explain to patients

- the risks of CRS and serious neurologic adverse reactions, associated with YESCARTA
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where YESCARTA was received for at least 4 weeks following YESCARTA infusion
- the need to carry the patient alert card at all times

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting, the applicant should conduct and submit a study based on a registry.	•Update reports: Annual safety reports and 5- yearly interim reports •Final report of study results: December 2038

The CHMP endorsed the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CAT review of the available data, the CAT considers that axicabtagene ciloleucel is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

The CHMP endorse the CAT conclusion on the new active substance status claim.