Application Type	BLA efficacy supplement
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Division / Office	DCGT/OTAT
Committee Chair	Mahat Upendra
Clinical Reviewer(s)	Mahat Upendra
Project Manager	Eden Chane
Priority Review	Yes
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Review Completion Date / Stamped Date	April 01, 2022
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Applicant	Novartis Pharmaceuticals Corporation
Established Name	Tisagenlecleucel
Trade Name	KYMRIAH™
Pharmacologic Class	CD19-directed genetically modified autologous T cell
Formulation(s), including Adjuvants, etc.	– Pediatric and Young Adult B-cell ALL (up to 25 years of age): A single dose of KYMRIAH contains 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 0.1 to 2.5 x 10^8 CAR positive viable T cells for patients more than 50 kg, suspended in one to three patient-specific infusion bag(s) for IV infusion. – Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma: A single dose of KYMRIAH contains 0.6 to 6.0 x 10^8 CAR-positive viable T cells suspended in one to three patient-specific infusion bag(s) for IV infusion
Dosage Form(s) and Route(s) of Administration	cell suspension for infusion.
Dosing Regimen	– Pediatric and Young Adult B-cell ALL (up to 25 years of age) o For patients 50 kg or less, administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight intravenously. o For patients above 50 kg, administer 0.1 to 2.5 x 10^8 total CAR positive viable T cells (non-weight based) intravenously. – Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma

	Administer 0.6 to 6.0 x 10^8 CAR-positive viable T cells intravenously.
Proposed Indication(s) and Intended Population(s)	Current: For treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. New: For treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Contents

Glossary

Abbreviation	Definition
ADR	Adverse drug reaction
ASTCT	American Society for Transplantation and Cellular Therapy
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
BCL-2	B-cell lymphoma-2
BOR	Best overall response
CAR-T	Chimeric antigen receptor T (cells)
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CRR	Complete response rate
CRS	Cytokine release syndromes
CSR	Clinical study report
CT	Computed tomography
CVP	Combination of cyclophosphamide, vincristine, and prednisone
DOR	Duration of response
DLBCL	Diffuse large B-cell lymphoma
EAS	EAS Efficacy analysis set
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FL	FL Follicular lymphoma
FDA	Food and Drug Administration
FL	Follicular lymphoma
HDT	high-dose therapy
IND	Investigational new drug
KM	Kaplan-Meier
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
R/R	Relapsed or refractory
SAE	Serious adverse event
SD	Stable Disease
ULN	Upper limit of normal

1. EXECUTIVE SUMMARY

KYMRIAH® (Tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. KYMRIAH is approved by FDA the indication of treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse (original BLA approved on August 30, 2017), and the indications of adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma (supplement BLA approval on May 01, 2018). The purpose of this BLA efficacy supplement was to support registration of tisagenlecleucel (Kymriah®, CTL019) for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of therapy.

The primary source of evidence to support the efficacy and safety of tisagenlecleucel in the adult r/r FL population in this supplemental BLA is the extended follow-up results of the Phase II single-arm, multicenter, open-label Study CCTL019E2202 (hereafter referred to as Study E2202) with a data cutoff date of March 29, 2021. Of a total of 98 enrolled subjects (enrolled set) of this cohort, 97 patients received infusion with KYMRIAH. Of the 97 patients infused with KYMRIAH, the first 90 patients with measurable disease who received KYMRIAH consecutively and had at least 9 months follow-up from first response or discontinued earlier constitute the primary efficacy analysis set, i.e., modified efficacy analysis set (mEAS).

The primary efficacy endpoint is complete response rate (CRR) as assessed by Independent Review Committee (IRC). Efficacy results summarized in this memo are based on a data cut-off date of March 29, 2021.

Sixty-one of the 90 patients in the mEAS population achieved complete response (CR) per IRC assessment. CRR was 67.8% (95% CI: 57.1, 77.2) and the lower limit of the 95% confidence interval was well above the pre-specified null hypothesis rate of 15%. Seventy-seven patients achieved CR or PR responses with an overall response rate (ORR) of 85.6% (95% CI:76.6, 92.1). The corresponding median duration of response (DOR) per IRC was not reached. Among all subjects in mEAS, the median PFS was 18.4 months (95% CI: 12.3, NE). The median overall survival (OS) was not reached. The median duration of follow-up was 17.1 months for subjects in mEAS from the time of the infusion to the data cut-off date (March 29, 2021).

The safety of Study E2202 was evaluated in all patients who received tisagenlecleucel (N=97) i.e., safety set. Deaths occurred in 7.2% (=7/97) of subjects in safety set. Serious adverse events (SAEs) which occurred any time post CTL019 infusion were reported in 43.3% (= 42/97) of subjects in safety set. The most common adverse event of special interest (AESI) was hematological disorders including cytopenias which occurred in 78.4% (=76/97) of subjects in the safety set.

The statistical analysis results for this supplemental BLA provides substantial evidence of effectiveness to support the approval of Tisagenlecleucel for the applicant's proposed indication of adult patients with r/r follicular lymphoma (FL) after two or more lines of therapy.

2. CLINICAL AND REGULATORY BACKGROUND

Tisagenlecleucel was granted Regenerative Medicine Advanced Therapy (RMAT) designations by FDA on April 20, 2020, for treatment of refractory or relapsed follicular lymphoma. Tisagenlecleucel was granted orphan-drug designation on 16-Sep-2020 for the treatment of follicular lymphoma.

The primary endpoint of the pivotal CCTL019E2202 (hereafter referred to as Study E2202) was met at the interim analysis (corresponding to a data cut-off date of May 26, 2020) when 52 patients were followed for at least 6 months post-infusion or had discontinued earlier, with a CRR of 65.4% (34/52 patients; 99.5% CI: 45.1, 82.4). This result was statistically significant at a 1-sided critical alpha level of 0.0025 to reject the null hypothesis (H_0) of CRR $\leqslant$ 15%. Furthermore, the results of the primary analysis (corresponding to a data cut-off date of 28-Sep-2020), conducted when 94 patients had either completed 6 months of follow-up or had discontinued for any reason, confirmed the efficacy of tisagenlecleucel, with a CRR per IRC in the EAS of 66.0% (95% CI: 55.5, 75.4).

On August 27, 2021, Novartis Pharmaceuticals Corporation submitted the supplemental Biologics License Application (sBLA)/Efficacy Supplement for Kymriah® (tisagenlecleucel) for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of therapy. The primary clinical evidence supporting the efficacy and safety of tisagenlecleucel for this indication is the extended follow-up of the pivotal Study E2202 with a data cutoff date of 29-Mar-2021 of this study.

On November 19, FDA issued a letter informing Novartis Pharmaceuticals Corporation that the amendment submitted and received on November 12, 2021, is considered a major amendment. An additional three months are therefore added to the original goal data and the new goal date is June 27, 2022. The updated datasets (i.e., ADRS_AD, Efficacy dataset: EFIRCAD and Time-to-event dataset: TTEIRCAD) were submitted to FDA on December 15, 2021.

Specifically, the statistical related update of the response status based on FDA clinical reviewer's evaluation are:

- Subject (b) (6): downgraded from Complete Response (CR) at Evaluation 2 on 02/03/2020 to Partial Response (PR).
- Subject (b) (6): downgraded from Partial Response (PR) at Evaluation 2 on 06/25/20 to Progressive Disease (PD).

As communicated during the pre-BLA meetings, FDA requested that the BLA should come with data for 90 consecutively treated FL patients with measurable disease by IRC at baseline, who have at least 9 months of follow up from the first objective response of PR/CR or would have discontinued earlier. Therefore, the FDA's primary efficacy analysis was performed in these 90 subjects which constitute the mEAS set.2.1 Disease or Health-Related Condition(s) Studied

2.1 Disease or Health-Related Condition(s) Studied

Follicular lymphoma (FL) is the second most common lymphoma diagnosed in the United States and Western Europe, accounting for approximately 20% of all NHLs, and 70% of indolent lymphomas [1]. The clinical course of follicular lymphoma is characterized by numerous periods of alternating remission and relapse with treatment efficacy and duration of remission declining with each successive therapy. Follicular lymphoma is considered incurable, and death generally occurs due to histological transformation to DLBCL or because FL becomes refractory to chemotherapy [2]. Moreover, patients with r/r FL will experience progressively shorter responses to subsequent treatments (second- or later lines of therapy). Cumulative toxicities from multiple therapies and resistance or transformation to high-grade or aggressive lymphomas are also major challenges in this population.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently available non-CAR-T therapies, which are given continuously or for several cycles, do not lead to high CRR and DOR in patients receiving third- or later lines of therapy. These therapies provide limited benefit to patients with FL in the third-line plus setting, with average CRRs in the range of 1% to 34%. There is also a medical need for improved treatment options that provide durable long-term disease control, thus reducing the need for subsequent anticancer treatments and associated toxicities (which can be cumulative) and the risk of histological transformation.

In the US, the recently approved CAR-T therapy, axicabtagene ciloleucel, has shown ORR > 90% and CR rates of 60% in the third- or later line setting, with a single infusion, in ZUMA-5 study, with durable response rates (Yescarta® USPIb).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1. summarizes the major regulatory activities for this sBLA.

Date	Milestone
30-Aug-2017	Approval of original BLA
01-May-2018	Approval of supplement BLA 125646/76
20-Apr-2020	Regenerative Medicine Advanced Therapy (RMAT) designation granted for the treatment of refractory or relapsed follicular lymphoma
16-Sep-2020	Orphan-drug designation granted for the treatment of follicular lymphoma

28-Sep-2020	Data cutoff date for Study E2202's Primary analysis
29-Mar-2021	Data cutoff date for Study E2202's Extended follow-up analysis
29-Jul-2021	Type B pre-sBLA meeting
27-Aug-2021	Efficacy supplement for Kymriah® (tisagenlecleucel) for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of therapy
20-Oct-2021	Filing letter issued to the Applicant
16-Nov-2021	Mid-cycle meeting with Applicant
19-Nov-2021	Major Amendment Acknowledgement letter sent to Novartis
15-Dec-2021	Updated dataset submitted with response to FDA's IR (dated 12/09/2021) regarding the major amendment.
27-June-2022	PDUFA action due date

(Source: FDA statistical reviewer's summary)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the product for the new indication comes from extended follow-up results of Study CCTL019E2202 (hereafter referred to as Study E2202), which is the focus of this review memo. The review of efficacy is based on the data cutoff date, March 29, 2021. The safety results are based on integrated safety datasets for Studies CCTL019C2201 and E2202, utilizing data cutoff dates of 11-Dec-2018 and 29-Mar-2021, respectively (Agreed by FDA on June 07, 2021).

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The focus of this statistical memo is the review of clinical study reports (CSR), datasets submitted in modules 2 and 5 of this BLA supplement, and the major amendment with updated datasets submitted on December 15, 2021.

5.3 Table of Studies/Clinical Trials

In addition to Study E2202, supportive safety data of adult patients with r/r FL were also analyzed from the pilot Phase IIa study CCTL019A2101J (hereafter referred to as Study A2101J). Table 2 summarizes the two studies included in this sBLA submission.

Extended follow-up results from Study E2202 formed the primary evidence of safety and efficacy of tisagenlecleucel for this sBLA.

Table 2. Studies in this sBLA submission

Study code	Study population	Study design	# of subjects treated
Pivotal study: E2202	adult patients with relapsed or refractory FL	Phase II, single-arm, multicenter open-label trial	97
Pilot study: A2101J	28 adult patients with lymphoma, including 14 patients with relapsed or refractory FL	Phase IIa, single-arm, single center, open-label trial	28

(Source: Clinical Overview, Table 1-2; FDA statistical reviewer's summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Pivotal study - Study E2202

Study E2202 is the pivotal study that constitutes the primary evidence of safety and efficacy of tisagenlecleucel in adult patients with r/r FL.

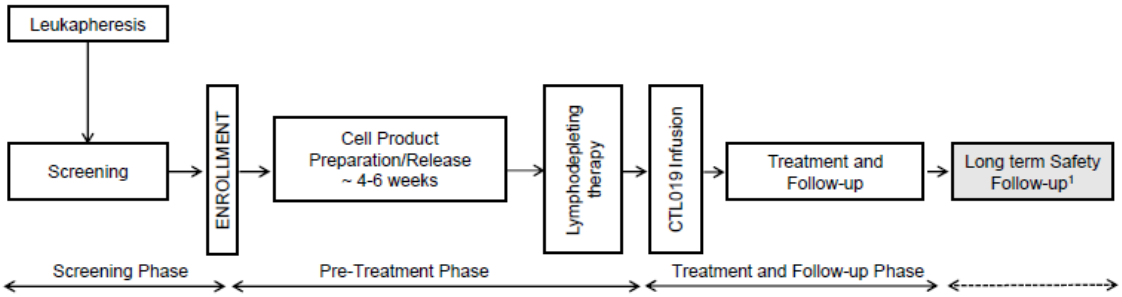
6.1.1 Objectives

Primary objective of the Phase 2 portion is to evaluate the efficacy of tisagenlecleucel therapy as measured by complete response rate determined by Independent Review Committee in the full analysis set based on Lugano 2014 classification response criteria [3].
Key secondary objectives were to evaluate the efficacy of tisagenlecleucel as measured by additional efficacy measures, including Overall Response Rate (ORR), Duration of Response (DOR), Progression Free Survival (PFS) and Overall Survival (OS).

6.1.2 Design Overview

Study E2022 is a Phase II, single arm, multicenter open-label trial to determine the efficacy and safety of tisagenlecleucel (CTL019) in adult patients with refractory or relapsed follicular lymphoma.
Approximately 113 adult patients with relapsed or refractory FL were planned to be enrolled to obtain 90 patients treated with tisagenlecleucel. Enrolled subjects were treated with a single dose of 0.6 to 6 x 10^8 CAR-positive viable T cells/kg. Figure 1 below gives an overview of the study flow chart.

Figure 1. Study flow chart



(Source: Module 5 of Clinical study report Figure 9-1, p.40)

6.1.3 Population

Key elements of eligibility criteria for Study E2202 are listed below:

- ⩾18 years of age with FL (grade 1, 2, 3A) confirmed histologically by central pathology review
- FL meeting one of the following criteria:
  - Refractory to a second or later line of systemic therapy (including anti-CD20 antibodies and alkylating agents) or relapsed within 6 months after completion of a second or later line of systemic therapy
  - Relapsed during anti-CD20 antibody maintenance (following at least 2 lines of therapy as above) or within 6 months after maintenance completion
  - Relapsed after autologous HSCT
- Radiographically measurable disease at screening
- ECOG performance score of 0 or 1 at screening
- Must have a leukapheresis product of non-mobilized cells accepted for manufacturing

6.1.4 Study Treatments or Agents Mandated by the Protocol

Tisagenlecleucel was administered via intravenous infusion as a single dose with a dose of 0.6 to 6.0 × 10^8 CAR-positive viable T cells.

6.1.6 Sites and Centers

This study was conducted in 32 sites, with patients enrolled and treated in 30 of these sites across 12 countries at the time of the data cut-off for this extended follow-up analysis.

6.1.7 Surveillance/Monitoring

The steering committee (SC) was established comprising investigators participating in the Trial and Novartis representatives from the Clinical Trial team to ensure transparent management of the study and perform review of safety data. The response status was evaluated by an Independent Review Committee (IRC) using the Lugano 2014 classification [3, 4].

6.1.8 Endpoints and Criteria for Study Success

In Study E2202, the primary endpoint is the CRR, defined as the proportion of patients with a best overall response of CR recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever comes first, assessed by IRC.

The study protocol also included the following secondary efficacy endpoints:

a. Overall response rate (ORR), including complete response (CR) and partial response (PR) determined by the independent review data in the Full Analysis Set based on the Lugano 2014 Classification, assessed by IRC.
b. Duration of response (DOR), achievement of CR or PR to relapse or death due to follicular lymphoma (FL), assessed by IRC.
c. DOR for CR only, defined as time from achievement of CR to relapse or death due to FL, assessed by IRC.
d. Progression-free survival (PFS), the time from tisagenlecleucel infusion to first documented disease progression or death due to any cause, assessed by IRC.
e. Overall survival (OS), time from date of first tisagenlecleucel infusion to date of death due to any reason. OS will be assessed in all patients (FAS).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical hypothesis:

H_0: CRR$\leqslant$15% vs. H_a: CRR>15%.

The threshold of 15% in the hypothesis is established based on the observed CRR of 14% in a recent study of idelalisib-treated patients with relapsed or refractory follicular lymphoma [5].

Analysis populations:

- *Efficacy analysis set (EAS):* The EAS comprised of all patients who received tisagenlecleucel and had measurable disease at baseline per IRC. Non-measurable disease at baseline is defined as absence of index lesion at baseline disease evaluation (i.e., no disease at baseline).
- *Modified efficacy analysis set (mEAS):* This set included the first 90 consecutively treated subjects who had measurable disease at baseline, received Tisagenlecleucel and had a minimum of 9 month follow up from first response (CR or PR) or have discontinued earlier (with the exception of one patient who has less than 9 months follow up due to COVID pandemic). This mEAS was defined by the clinical reviewer and was used for all efficacy analyses in this review memo.
- *Safety Set:* all patients who received a tisagenlecleucel infusion. The Safety set was used for all safety analyses.
  Note: The Safety set is also the Tisagenlecleucel infused set.
- *Per-protocol set (PPS)*: The PPS consisted of a subset of patients in the EAS who had a diagnosis of FL at baseline and received the recommended dose.

- *Cellular kinetic analysis set (CKAS):* patients in the EAS who provided an evaluable cellular kinetic profile (at least 1 cellular kinetic parameter).
- *Tocilizumab pharmacokinetic analyses set (TPAS):* this set consisted of patients in the Tisagenlecleucel infused set who took at least one dose of tocilizumab and provided at least one tocilizumab PK concentration.

Statistical methods:
Efficacy analyses were conducted on the mEAS population by the IRC assessment. Using the data of 90 consecutively treated FL patients with measurable disease by IRC at baseline, who have at least 9 months of follow up from the first objective response of PR/CR or would have discontinued earlier (i.e., mEAS) for primary efficacy analysis was an agreement made between FDA and the applicant before this BLA submission.

Primary endpoint
The primary efficacy endpoint, CRR, was calculated along with the 2-sided 95% exact Clopper-Pearson confidence interval (CI). The p-value from a 1-sided exact binomial test with significant level of 0.025 for the null hypothesis of CRR $\leqslant$15% was provided.

Secondary endpoints

a. ORR: the rate and its 2-sided 95% exact Clopper-Pearson exact CI were estimated.
b. DOR: The Kaplan-Meier (KM) method was used to estimate the median DOR along with the 95% CI. The reverse KM method was used to estimate the median follow-up time for DOR with the 95% CI. Proportion of patients without event at 3, 6, 9, and 12 months was estimated along with 95% confidence interval.
c. PFS: The analysis of PFS was conducted similarly to the analysis of DOR.
d. OS: The distribution function of OS was estimated using the Kaplan Meier (KM) method. The median OS and the proportion of patients alive at 3, 6, 12, 18, and 24 months with 95% confidence intervals were presented.

Interim analyses:
One interim analysis was previously performed with data cut-off 05/26/2020 and 52 patients were included in the analysis. The primary endpoint was met in this interim analysis. By the time of the interim analysis, enrollment into the study was completed and all enrolled patients were treated or discontinued prior to infusion. Therefore, the study was not stopped for outstanding efficacy.

Sample size and power calculation:
With 90 subjects treated with tisagenlecleucel in the primary analysis of the study, the study achieves 90% power to test the null hypothesis that the ORR is 15% vs. the alternative hypothesis that the ORR is 30% at a 1-sided alpha level of 0.025.

Sensitivity analyses:

Sensitivity analyses of the primary efficacy endpoints CRR were performed based on the enrolled set, safety set, and PPS using the same methodology, as well as on the EAS and EAS excluding patients who achieved CR at the radiologic assessment at baseline per IRC.

Subgroup analyses:
The following subgroups of interest were used for the supporting efficacy analysis of the CRR. Subgroup analyses will only be performed if at least 5 patients are present in each subgroup. Grouping of classes will be considered if there are too few patients in some subgroups.

- Age: < 65, and ≥ 65 years at the time of the first infusion
- Sex: male vs. female
- Race: White, African American and other races
- Ethnicity: Hispanic or Latino, Chinese, Indian, Japanese, Mixed ethnicity, Other
- FLIPI at enrollment: low/intermediate, high
- FL grade: 1, 2, 3
- Number of prior lines of anti-neoplastic therapy: ≤2 lines, 3 to 4 lines, >4 lines
- PI3K inhibitor use: naïve, pretreated
- Prior HSCT therapy: yes or no. In addition, patients who relapsed ≤ 12 months from HSCT and >12 months from HSCT was displayed.
- Disease status to last line of prior anti-neoplastic therapy: refractory, relapsed
- Progression of disease within 24 months (POD24) from initiation of first-line anti-CD20 mAb containing therapy: yes, no
- Bulky disease at baseline (defined per IRC as imaging showing any nodal or extra nodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm): yes or no
- Bridging therapy: yes or no
- LDH at study entry: ≤ ULN or >ULN
- R2 use (lenalidomide + rituximab, within same regimen): naïve, pretreated
- US sites: yes, no
- TMTV at baseline: Low tumor burden (tumor volume ≤ 510 cm^3 or high tumor burden (tumor volume >510 cm^3)
- Double refractory (defined as patients who failed to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen): yes, no

Missing data:
All subjects who were of unknown clinical response were treated as non-responders.
For assessment of DOR, PFS and OS, loss to follow-up subjects would be censored at the date of the last evaluable disease assessment prior to the data cutoff date.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

For analyses of efficacy and safety in Study E2202, table 3 below summarizes the numbers of patients in each analysis set. There are 98 enrolled subjects. 97 (99.0%) patients who received a tisagenlecleucel infusion constituted the safety analysis set (this is also the Tisagenlecleucel infused set). Of the 97 infused patients, 90 patients who had measurable disease at baseline and had at least 9 months of follow up from first response or discontinued earlier per IRC constituted the primary efficacy analysis set.

Table 3. Analysis sets

Analysis set	All Patients N=98 n (%)
Enrolled set	98 (100)
Tisagenlecleucel infused set	97 (99.0)
Safety set	97 (99.0)
Efficacy analysis set	94 (95.9)
Modified efficacy analysis set	90 (91.8)
Per-protocol set	85 (86.7)
Cellular kinetic analysis set	94 (95.9)
Tocilizumab cellular kinetic analysis set	11 (11.2)

(source: Table 10-2 on page 65 of CSR)

6.1.10.1.1 Demographics

Table 4 shows the demographic information for the study in the Enrolled, Safety set and mEAS.

Table 4. Demographics for enrolled set and mEAS

Demographic variable	Enrolled set N=98 n (%)	Safety set N=97 n (%)	mEAS N=90 n (%)
Age (years)			
<65	74 (75.5)	73 (75.3)	66 (73.3)
≥65	24 (24.5)	24 (24.7)	24 (26.7)
Mean (STD)	56.5 (10.3)	56.5 (10.4)	56.7 (10.6)
Median (min, max)	57.5 (29.0, 73.0)	57.0 (29.0, 73.0)	58.0 (29.0, 73.0)
Sex n (%)			
Female	33 (33.7)	33 (34.1)	28 (31.1)
Male	65 (66.3)	64 (66.0)	62 (68.9)
Race n (%)			
Asian	13 (13.3)	13 (13.4)	9 (10.0)
Black or African American	1 (1.0)	1 (1.0)	1 (1.1)
White	74 (75.5)	73 (75.3)	70 (77.8)
Not reported	2 (2.0)	10 (10.3)	10 (11.1)
Ethnicity n (%)			
Hispanic or Latino	3 (3.1)	2 (2.1)	2 (2.2)
Not Hispanic or Latino	84 (85.7)	84 (86.6)	77 (85.6)
Not reported	11 (11.2)	11 (11.3)	11(12.2)

(Source: Reviewer's analysis)

6.1.10.1.2 Baseline disease characteristics

Table 5 shows the baseline disease characteristics were consistent across the Enrolled set, Safety set and mEAS. Most of the patients presented with advanced FL (Stage III or IV) at study entry. Patients were heavily pretreated with multiple prior lines of antineoplastic therapy.

Table 5. Baseline disease characteristics for enrolled and mEAS

Disease history	Enrolled set N=98 n (%)	Safety set N=97 n (%)	mEAS N=90 n (%)
Diagnosis of disease – n (%) Follicular lymphoma	98 (100)	97 (100)	90 (100)
Stage at initial diagnosis – n (%)			
I	6 (6.1)	6 (6.2)	5 (5.6)
II	13 (13.3)	13 (13.4)	13 (14.4)
III	21 (21.4)	21 (21.6)	19 (21.1)
IV	57 (58.2)	56 (57.7)	52 (57.8)
Missing	1 (1.0)	1 (1.0)	1 (1.1)
Stage at time of study entry – n (%)			
I	3 (3.1)	3 (3.1)	2 (2.2)
II	11 (11.2)	11 (11.3)	10 (11.1)
III	26 (26.5)	25 (25.8)	25 (27.8)
IV	58 (59.2)	58 (59.8)	53 (58.9)

Bone marrow involved at study entry – n (%)			
Yes	37 (37.8)	37 (38.1)	35 (38.9)
No	60 (61.2)	59 (60.8)	54 (60.0)
Missing	1 (1.0)	1 (1.0)	1 (1.1)
Histological grade at study entry – n (%)			
Grade 1-2 (low grade)	88 (89.8)	87 (89.7)	81 (90.0)
Grade 3A	10 (10.2)	10 (10.3)	9 (10.0)
Were any extra lymphatic sites involved by lymphoma at study entry – n (%)			
Yes	30 (30.6)	30 (30.9)	27 (70.0)
No	68 (69.4)	67 (69.1)	63 (30.0)
FLIPI at study entry – n (%)			
Low	18 (18.4)	18 (18.6)	16 (17.8)
Intermediate	21 (21.4)	21 (21.6)	18 (20.0)
High	59 (60.2)	58 (59.8)	56 (62.2)
Absolute lymphocyte count (ALC) at study entry (10^9/L)			
N	97	94	90
Mean (SD)	2.4 (1.51)	2.4 (1.53)	2.4 (1.55)
Median (min-max)	1.9 (0.2-7.0)	1.9 (0.2-7.0)	1.95 (0.1, 7.0)
Number of prior lines of antineoplastic therapy			
Median (min – max)	4.0 (2.0 – 13.0)		
Number of prior lines of antineoplastic therapy – n (%)			
2	24 (24.5)	24 (24.7)	22 (24.4)
3	21 (21.4)	21 (21.6)	19 (21.1)
4	25 (25.5)	25 (25.8)	22 (24.4)
≥5	28 (28.6)	27 (27.8)	27 (30.0)
Progression of disease within 24 months (POD24)2 from first-line anti-CD20 mAb containing therapy - n (%)			
POD24 group	61 (62.2)	61 (62.9)	59 (65.6)
Non-POD24 group	36 (36.7)	36 (37.1)	31 (34.4)
Missing	1 (1.0)	0	0
Bulky disease at baseline - n (%)			
Yes	62 (63.3)	62 (63.9)	58 (64.4)
No	36 (36.7)	35 (36.1)	32 (35.6)
Treatment density			
Mean (SD)	1.73 (1.17)	1.73 (1.17)	1.65 (1.16)
Median (min-max)	1.40 (0.14 – 5.65)	1.41 (0.14, 5.65)	1.31 (0.14, 5.65)

(Source: Table 10-4 on page 66-68 CSR, section 10.4.2; reviewer's analysis)

6.1.10.1.3 Subject Disposition

At the time of the data cutoff date March 29, 2021, 98 patients were enrolled in the study. 97 of the enrolled patients received their tisagenlecleucel infusion and one patient without measurable disease was ineligible to receive tisagenlecleucel infusion. Of the 97 infused patients, 80 patients were ongoing in the study at the time of the cut-off and 17 patients

had discontinued the study. The most common reason for discontinuation was death (n=7). The detailed subject disposition is shown in table 6 below.
Note that, of the 97 patients infused with KYMRIAH, the primary efficacy analysis population included the first 90 patients with measurable disease who received KYMRIAH consecutively and had at least 9 months follow-up from first response or discontinued earlier.

Table 6. Study disposition for Enrolled set

	All patients N=98 n (%)
Patients enrolled	**98 (100.0)**
Patients treated	97 (99.0)
Discontinued prior to tisagenlecleucel infusion	1 (1.0)
Reason for discontinuation	
Physician decision	1 (1.0)
Study ongoing	80 (81.6)
Discontinued study	18 (18.4)
Reason for discontinuation	
Death	7 (7.1)
Physician decision	5 (5.1)
Subject decision	5 (5.1)
Lost to follow-up	1 (1.0)

(source: page 19 of summary of clinical efficacy, section 3.1.1.1)

6.1.11 Efficacy Analyses

6.1.11.1 Analysis of Primary Endpoint(s)

With the current data cut-off date (March 29, 2021) for the extended follow-up of E2202, the CRR per IRC and local Investigator assessment for all the analysis sets are shown in Table 7 below.

Ninety patients in the mEAS form the basis of the efficacy analysis and 61 of the 90 patients achieved response of CR based on IRC assessment. The CRR per IRC assessment was 67.8% (95% CI: 57.1, 77.2). The lower limit of the 95% exact Clopper-Pearson confidence interval for CRR was 57.1% which is well above the pre-specified null hypothesis rate of 15%. The CRR per local Investigator assessment in the mEAS was 72.2% (95% CI: 61.8, 81.1), which is consistent with the IRC assessment. The CRR results analyzed across different analysis sets were also consistent with those of the mEAS.

Table 7. CRR per IRC and local Investigator assessment (mEAS, Enrolled set, Tisagenlecleucel infused set, EAS and PPS)

	IRC assessment		**Local assessment**	
CRR	**n (%)**	**95% CI**	**n (%)**	**95% CI**
mEAS (N=90)	**61 (67.8)**	**(57.1, 77.2)**	**65 (72.2)**	**(61.8, 81.1)**
Enrolled set (N=98)	66 (67.3)	(57.1, 76.5)	70 (71.4)	(61.4, 80.1)
Tisagenlecleucel infused set (N=97)	66 (68.0)	(57.8, 77.1)	70 (72.2)	(62.1, 80.8)
EAS (N=94)	65 (69.1)	(58.8, 78.3)	68 (72.3)	(62.2, 81.1)
PPS (N=85)	61 (71.8)	(61.0, 81.0)	64 (75.3)	(64.7, 84.0)

(Source: reviewer's analysis)

6.1.11.2 Analyses of Secondary Endpoints

There's no formal hypothesis testing planned for these secondary endpoints. Analysis of these secondary endpoints were conducted based on updated datasets submitted on December 15, 2021.

Overall response Rate

The ORR was 85.6% (77 patients, 95% CI: 76.6, 92.1) per IRC assessment and 90.0% (81 patients, 95% CI: 81.9, 95.3) per local Investigator assessment in the mEAS. The ORR for the other analysis sets (Enrolled set, Tisagenlecleucel infused set, EAS and PPS) are also shown in Table 8 below.

Table 8. ORR per IRC and local Investigator assessment (mEAS, Enrolled set, Tisagenlecleucel infused set, EAS and PPS)

	IRC assessment		**Local assessment**	
ORR (CR+PR)	**n (%)**	**95% CI**	**n (%)**	**95% CI**
mEAS (N=90)	77 (85.6)	(76.6, 92.1)	81 (90.0)	(81.9, 95.3)
Enrolled set (N=98)	84 (85.7)	(77.2, 92.0)	88 (89.8)	(82.0, 95.0)
Tisagenlecleucel infused set (N=97)	84 (86.6)	(78.2, 92.7)	88 (90.7)	(83.1, 95.7)
EAS (N=94)	81 (86.2)	(77.5, 92.4)	85 (90.4)	(82.6, 95.5)
PPS (N =85)	74 (87.1)	(78.0, 93.4)	78 (91.8)	(83.8, 96.6)

(Source: Table 11-3, CSR section 11.1.1, page 74; Reviewer's analysis)

Different responses per IRC and local assessment of the mEAS are shown in Table 9.

Table 9. Different responses per IRC and Local assessment

	IRC assessment		**Local assessment**	
	n (%)	**95% CI**	**n (%)**	**95% CI**
CR	61 (67.8)	(57.1, 77.2)	65 (72.2)	(61.8, 81.1)
PR	16 (17.8)	(10.5, 27.3)	16 (17.8)	(0.11, 0.27)
SD	3 (3.2)	(0.01, 0.09)	3 (3.3)	(0.01, 0.09)
PD	9 (9.6)	(0.05, 0.18)	6 (6.7)	(0.02, 0.14)
Unknown	1 (1.1)	(0.00, 0.06)	0 (0.0)	(0.00, 0.04)

(Source: reviewer's analysis)

Duration of response (DOR)

Per IRC review in the mEAS, DOR was calculated for the 77 patients who achieved CR or PR. The median DOR was not reached. The probabilities of remaining in response at 9 months and 12 months were 74.9% (95% CI: 63.5, 83.3) and 70.5% (95% CI: 57.9, 80.0), respectively. The KM plot of DOR per IRC assessment is presented in Figure 2. The DOR was also calculated for the 81 patients who achieved CR or PR per local investigator assessment in the mEAS. The results are similarly shown in the last column in Table 10.

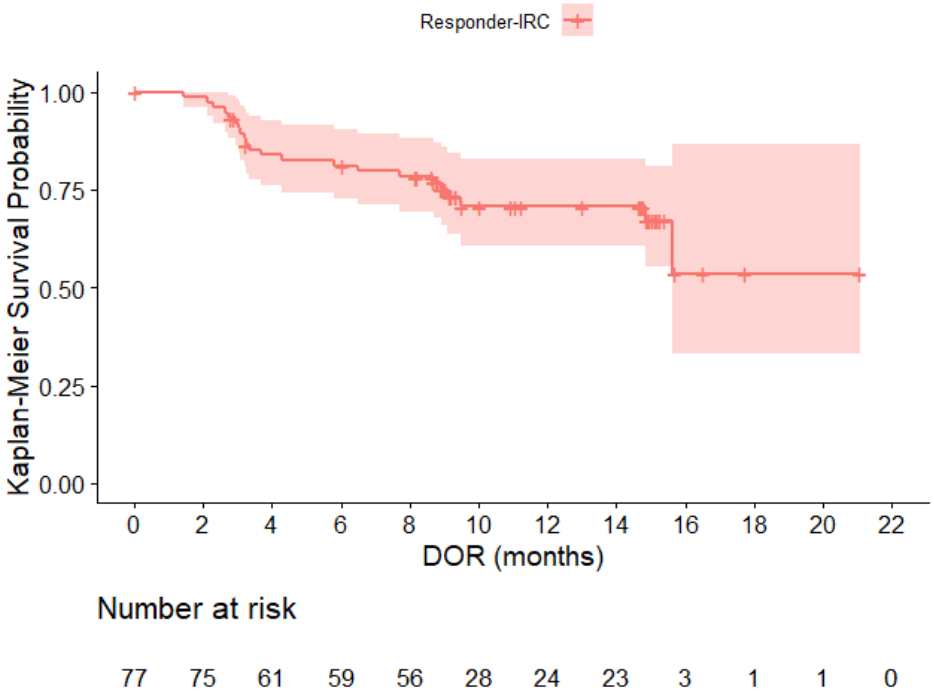
Table 10. DOR results per IRC and local Investigator assessment (mEAS) for patients with best overall response of CR or PR

	IRC assessment	local Investigator assessment
Events[1]/patients (%)	22/77 (28.6)	23/81 (28.4)
Percentiles (95% CI)		
25th	9.1 (3.3, 15.6)	9.1 (3.3, 15.6)
50th	NE (15.6, NE)	15.6 (15.3, NE)
75th	NE (NE, NE)	NE (15.6, NE)
% Event-free probability estimates (95% CI)[2]		
Month 3	92.1 (83.2, 96.4)	92.4 (83.8, 96.5)
Month 6	81.1 (70.2, 88.4)	79.4 (68.6, 86.9)
Month 9	75.2 (63.5, 83.6)	75.1 (63.7, 83.3)
Month 12	70.8 (58.0, 80.3)	73.1 (61.3, 81.9)
Month 15	67.1 (52.6, 78.0)	70.3 (57.5, 79.9)

[1]Event: progression and/or death.
[2]% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the KM survival estimates.
(Source: reviewer's analysis of DOR)

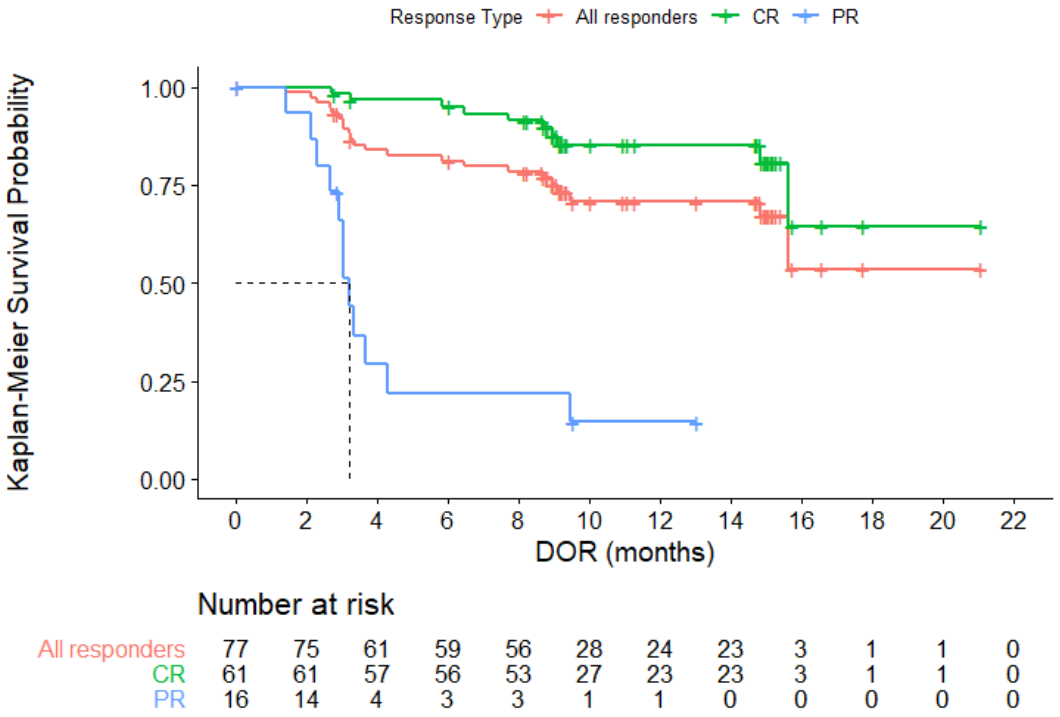
KM curves of DOR by best CR and PR per IRC assessment is presented in Figure 3. Duration of response for subjects with CR appears to be longer compared to that for PR.

Figure 2. Kaplan-Meier curves of DOR for responders (CR or PR) per IRC in mEAS.



(Source: FDA statistical reviewer's analysis)

Figure 3. Kaplan-Meier curves of different responses per IRC (mEAS)



(Source: FDA statistical reviewer's analysis)

Progression-free Survival (PFS)

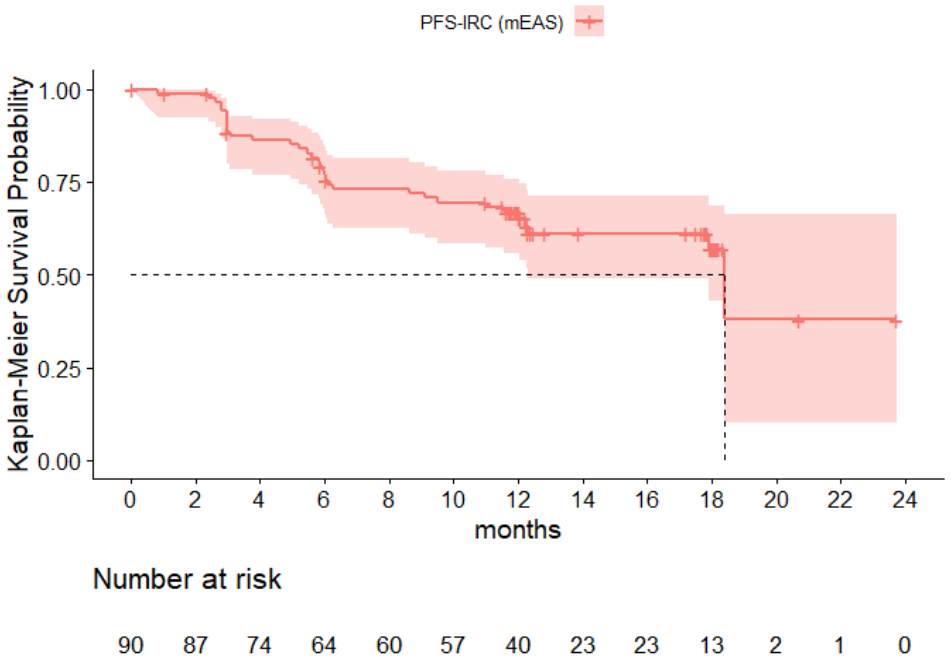
Table 14 summarizes the PFS results for mEAS based on IRC and local Investigator assessments, respectively. There were 33 PFS events (disease progression or death) in total per IRC. The estimated 12-month progression free survival probability was 67.0% (95% CI: 55.8, 75.9) per IRC. The median PFS per IRC was 18.4 months (95% CI: 12.3, NE) with a lower limit of the 95% confidence limits at 12.3 months and an upper limit unattainable. The KM plot of PFS per IRC assessment is presented in Figure 4.

Table 14. PFS results in m*EAS* (N=90)

	IRC assessment	local Investigator assessment
Event*/patients (%)	33/90 (36.7)	32/90 (35.6)
Percentiles (95% CI)	(26.8, 47.5)	(25.7, 46.3)
25th	6.1 (5.2, 12.1)	6.2 (5.7, 12.3)
50th	18.4 (12.3, NE)	18.4 (15.6, NE)
75th	NE (18.4, NE)	NE (18.4, NE)
% PFS probability estimates (95% CI)		
Month 3	88.5 (79.7, 93.7)	90.8 (82.5, 95.3)
Month 6	76.8 (66.3, 84.4)	78.1 (67.9, 85.5)
Month 9	71.9 (61.1, 80.2)	73.4 (62.8, 81.5)
Month 12	67.0 (55.8, 75.9)	68.6 (57.6, 77.3)
Month 15	61.1 (49.0, 71.2)	64.9 (53.2, 74.3)
Month 18	57.0 (43.1, 68.8)	62.3 (49.9, 72.4)

*Event: progression and/or death
(Source: FDA statistical reviewer's analysis)

Figure 4. Kaplan-Meier Curves of PFS per IRC for m*EAS*



(Source: FDA statistical reviewer's analysis)

Overall Survival (OS)

The median OS was not reached at the time of the data cut-off date. Six deaths had occurred in the study for subjects in the mEAS. The estimated probability of survival was

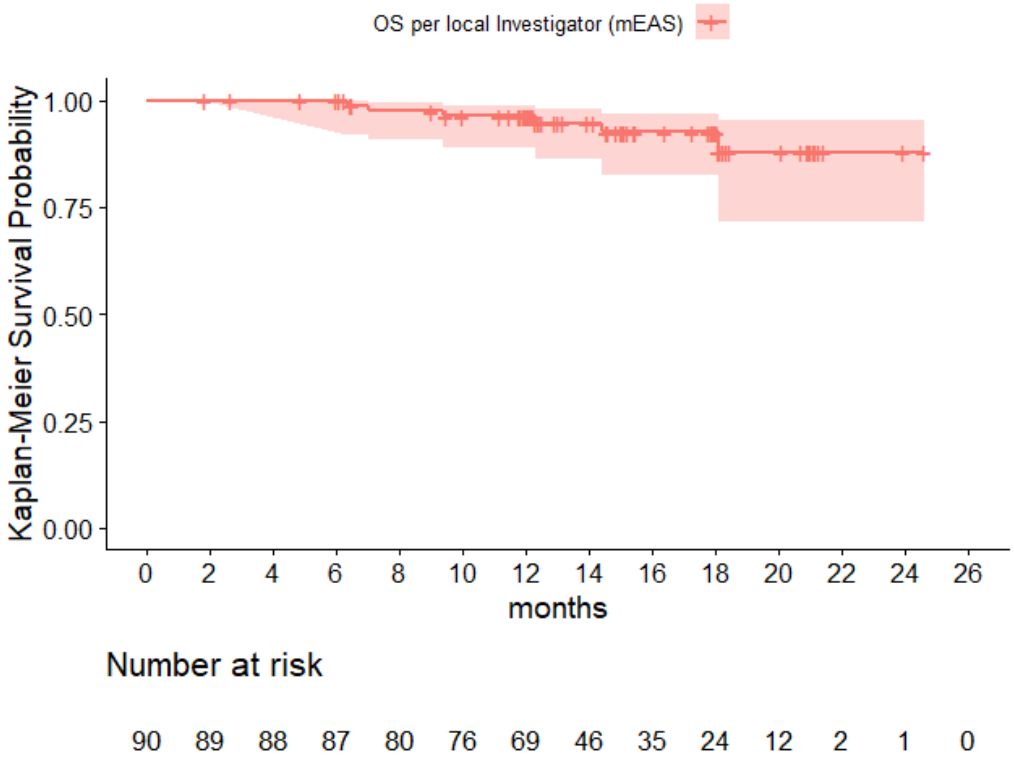
96.4% (95% CI: 89.1, 98.8) at Month 12 and 92.6% (95% CI:82.6, 96.9) at Month 18. The OS results are shown in table 15 and the overall K-M curves are shown in Figure 6.

Table 15. OS results in m*EAS* (N=90)

Death/patients (%)	6/90 (6.7)
Percentiles (95% CI)	
25th	NE (18.1, NE)
50th	NE
75th	NE
% Survival probability estimates (95% CI)	
Month 3	100
Month 6	100
Month 9	97.7 (90.7, 99.4)
Month 12	96.4 (89.1, 98.8)
Month 15	92.6 (82.6, 96.9)
Month 18	92.6 (82.6, 96.9)

(Source: Table 14 on page 33, section 4.3.6 of Updated Efficacy; reviewer's analysis)

Figure 6. Kaplan-Meier Curves for Overall Survival (mEAS)

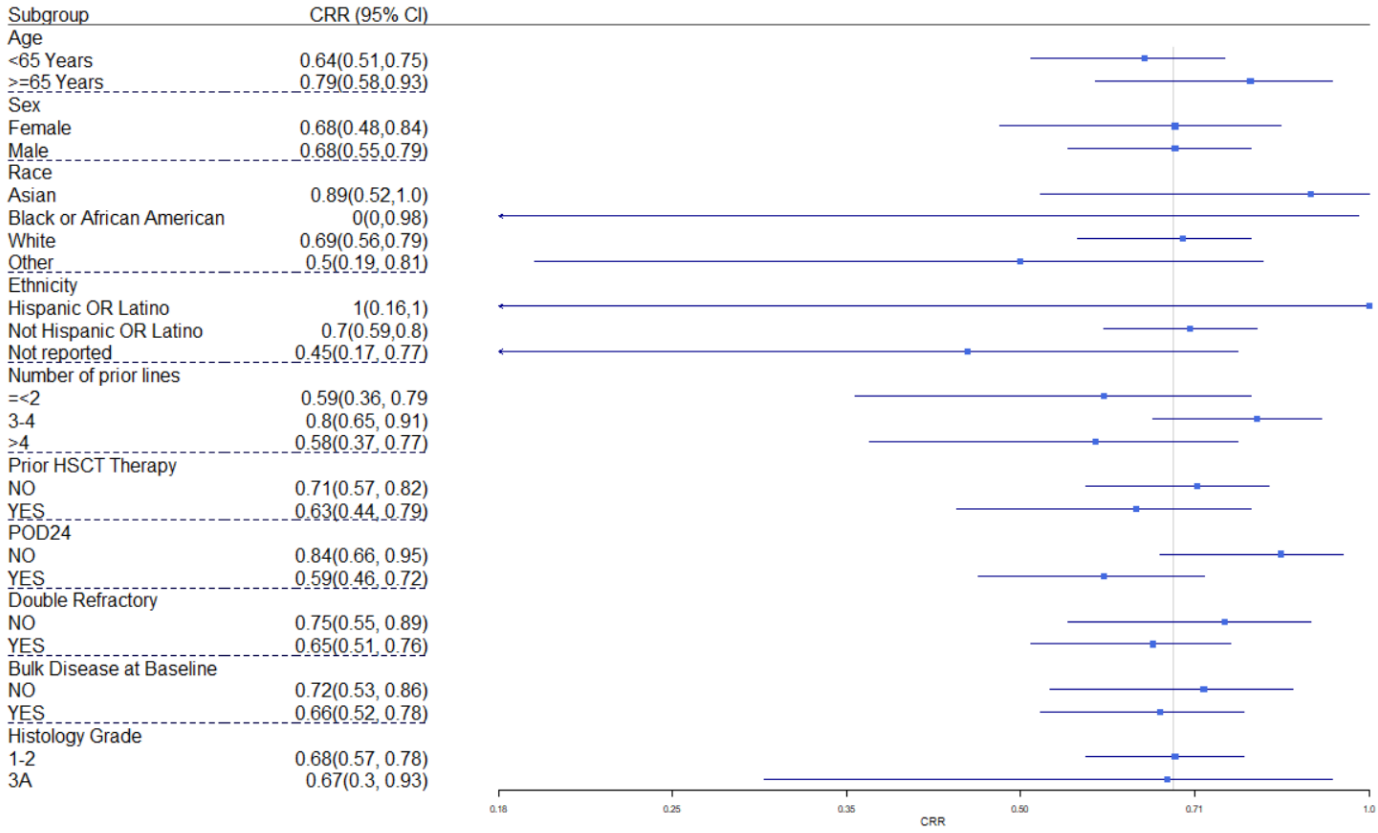


(Source: FDA statistical reviewer's analysis)

6.1.11.3 Subpopulation Analyses

Figure 7 shows the forest plot of CRR per IRC assessment in m*EAS* across baseline characteristic subgroups by age, sex, race, and other baseline factors. Robustness of CRR was further confirmed by a series of predefined sensitivity analyses, with CRRs ranging from 59% to 66% across different high risk subgroups, i.e., patients who were double refractory, patients with high FLIPI, bulky disease at baseline and patients belonging to POD24 group. The lower limit of 95% exact Clopper-Pearson confidence interval for CRR is above the null hypothesis rate of 15% for each subgroup.

Figure 7. Forest plot of CRR per IRC by subgroup (mEAS)



(Source: FDA statistical reviewer's analysis)

6.1.11.4 Discontinuations

Table 16 summarizes subjects' discontinuations status from the study. A total of 98 patients were enrolled in the study and 97 patients were infused. Of the infused patients, 80 patients were in follow-up in the study at the time of the data cut-off and 17 patients had discontinued the study.

Table 16. Subjects' discontinuations

Patients enrolled	98 (100%)
Discontinued prior to tisagenlecleucel infusion-Physician decision	1 (1.0%)
treatment received	97 (99.0%)
Follow-up ongoing	80 (81.6%)
Discontinued	17 (17.3%)
Reason for discontinuation	
Death	7 (7.1%)
Physician decision	4 (4.1%)
Subject decision	5 (5.1%))
Lost to follow-up	1 (1.0%)

(Source: reviewer's summary; Table 10-1, page 63 of CSR)

6.1.12 Safety Analyses

This section summarizes safety results of Study E2202 based on the safety data with cutoff date of March 29, 2021.

6.1.12.1 Methods

Descriptive statistic was used to summarize safety data for Study E2022. For data summary, the primary analysis population for all safety analyses was all treated population which included all 97 subjects who received LD chemotherapy.

6.1.12.3 Deaths

Deaths at the time of the 29-Mar-2021 data cut-off date in the safety analysis set are listed in Table 17. Among the 97 all-treated subjects, 7 (7.2%) subjects died with all deaths occurring >30 days post-tisagenlecleucel infusion. Five patients died due to progression of the underlying disease. The other two fatalities occurred approximately 1 year post tisagenlecleucel infusion.

Table 17. Deaths reported in the safety analysis set (i.e., all treated analysis set)

	N (%)
All-treated	97
Total number of subjects who died during study	7 (7.2%)
Cause of death	
Progressive Underlying Disease	5 (5.2%)
AE/Cytokine release syndrome	1 (1.0%)
Euthanasia	1 (1.0%)

(Source: reviewer's summary, CSR p.105 section 12.2.1)

6.1.12.4 Serious Adverse Events

Serious adverse events were reported for 42 subjects (43.3%) in *Safety Set (N=97)*. The most frequently reported SAEs were CRS (n=19, 19.6%), Pneumonia (n=8, 8.2%) and Febrile neutropenia (n=6, 6.2%).

Table 18 summarizes the SAEs reported anytime post-tisagenlecleucel infusion, irrespective of study drug relationship, by PT and maximum grade, and reported in at least 2 patients (Safety set).

Table 18. SAEs reported in at least 2 patients (Safety set)

	All patients N=97	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of subjects with at least one event	**42 (43.3)**	**25 (25.8)**
Cytokine release syndrome	19 (19.6)	1 (1.0)
Pneumonia	8 (8.2)	5 (5.2)
Febrile neutropenia	6 (6.2)	6 (6.2)
Pyrexia	3 (3.1)	0
Encephalopathy	2 (2.1)	1 (1.0)
Infusion related reaction	2 (2.1)	2 (2.1)
Neutropenia	2 (2.1)	2 (2.1)
Pleural effusion	2 (2.1)	0
Squamous cell carcinoma	2 (2.1)	0

(Source: Clinical study report p.106, Table 12-6)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 19 summarizes the AESI anytime post-tisagenlecleucel infusion, suspected to be treatment related, by PT and maximum grade and occurring in more than 5% of patients (Safety set). CRS occurred most frequently in 49.5% (=48/97) of the 97 adult patients with r/r FL receiving KYMRIAH. CRS events in 19 patients were considered serious. Thirteen episodes of Serious neurological adverse reactions (SNARs) including both non-serious and serious AEs were reported in 11 patients (11.3%) post-tisagenlecleucel infusion. The median time to onset of the first SNAR was 9.0 days (range: 4 to 345). 78.4% (76/97) of the 97 patients had hematological disorders including cytopenias, mostly of Grade ⩾ 3 (74.2%) severity. Most events occurred within 8 weeks post-tisagenlecleucel infusion (75.3%). Infections occurring at any time post-infusion were reported in 48 patients (49.5%), 13 of whom (13.4%) had infections suspected to be related to tisagenlecleucel. The majority of the patients had infections either within 8 weeks (18.6%) or in the period from >8 weeks to 1-year post-tisagenlecleucel infusion (38.5%). Only 5 patients had infections more than 1 year after the infusion. Post-tisagenlecleucel infusion, 16 patients (16.5%) had AEs of prolonged depletion of normal B-cells/agammaglobulinemia; AEs in 10 patients (10.3%) were suspected to be related to tisagenlecleucel. Tumor lysis syndrome was reported in 2 patients (2.1%), and one of these events was suspected to be related to tisagenlecleucel.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Tisagenlecleucel is a CD19-directed genetically modified autologous T cell immunotherapy. The purpose of the extended follow-up analysis of Study E2202 was to demonstrate efficacy and safety in the patient population with r/r FL. Of the 98 enrolled subjects in this study, 97 subjects received tisagenlecleucel infusion. These 97 subjects constituted the safety analysis set and were the basis for safety analyses. Of the 97 infused patients, the 90 consecutively treated FL patients with measurable disease by IRC at baseline, who have at least 9 months of follow up from the first objective response of PR/CR or would have discontinued earlier, constitute the set for primary efficacy analysis, per the agreement before the BLA submission.
The pre-specified primary efficacy endpoint is complete response rate (CRR), defined as the proportion of patients with a BOR of CR recorded from tisagenlecleucel infusion until progressive disease or start of new anticancer therapy, whichever came first per IRC assessment. Efficacy and safety results summarized in this memo are based on a data cut-off date of March 29, 2021.

The CRR as assessed per IRC in the mEAS was 67.8% (95% CI: 57.1, 77.2) and the lower limit of the 95% exact Clopper-Pearson confidence interval of 57.1% was well above the pre-specified null hypothesis rate of 15%. The ORR was 85.6% (81 patients, 95% CI: 76.6, 92.1) per IRC assessment, with 61 subjects (67.8%) who achieved complete response and 16 patients (17.8%) who achieved PR. Median duration of response (DOR) per IRC was not reached. The probabilities of the responders (i.e., CR or PR per IRC) remaining in response at 9 months was 75.2% (95% CI: 63.5, 83.6). There were 33 PFS events (33/90, 36.7%) in total (disease progression or death) in mEAS. The estimated progression free probability was 67.0% (95% CI: 55.8, 75.9) at Month 12. The estimated probability of overall survival was 96.4% (95% CI:89.1, 98.8) at Month 12 and 92.6% (95% CI:82.6, 96.9) at Month 18 for mEAS.

Deaths occurred in 7.2% (= 7/97) of treated subjects who received tisagenlecleucel (safety set). SAEs were reported in 43.3% (= 42/97) of treated subjects. CRS occurred in 19 (19.6%) subjects.

10.2 Conclusions and Recommendations

The statistical analysis results provide sufficient evidence of effectiveness to support the approval of tisagenlecleucel for the proposed indication of adult patients with relapsed or refractory follicular lymphoma.

11. REFERENCES

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