Application Type	Original BLA
STN	125646/0
CBER Received Date	February 2, 2017
PDUFA Goal Date	October 3, 2017
Division / Office	DCGT /OTAT
Committee Chair	Victor (Xiaobin) Lu
Clinical Reviewer(s)	Maura C. O'Leary; Donna Przepiorka
Project Manager	Erica L. Giordano
Priority Review	Yes
Reviewer Name(s)	Xue Lin, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Shiowjen Lee, Ph.D. Team Leader, FDA/CBER/OBE/DB/TEB
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	John Scott, Ph.D. Acting Director, FDA/CBER/OBE/DB
Applicant	Novartis
Established Name	Tisagenlecleucel-T
Trade Name	KYMRIAH
Pharmacologic Class	CD19-directed genetically-modified autologous T cell
Formulation(s), including Adjuvants, etc	Comprised of genetically-modified antigen-specific autologous T cells that have been reprogrammed to target cells that express CD19. In addition, the product also contains Plasmalyte-A, Dextrose, sodium chloride (NaCl), Dextran 40 in Dextrose, Human Serum Albumin (HSA), and dimethylsulfoxide (DMSO)
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	2.0 to 5.0 x10^6 transduced viable T cells per kg body weight (for patients $\leq$ 50 kg) and

	1.0 to 2.5 x 10^8 transduced viable T cells (for patients > 50 kg)
Indication(s) and Intended Population(s)	Indicated in combination with lymphodepleting chemotherapy for the treatment of pediatric and young adult patients (age 3-25 years) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

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GLOSSARY

ALL acute lymphoblastic leukemia
BLA Biologics Licensure Application
BOR best overall response
CAR chimeric antigen receptor
CI confidence interval
CR complete remission
CRi complete remission with incomplete hematologic recovery
CRS cytokine release syndrome
CSR clinical study report
DOR duration of remission
EAS efficacy analysis set
EFS event-free survival
FAS full analysis set
IEAS interim efficacy analysis set
IRC independent review committee
IV intravenous
MRD minimal residual disease
ORR overall remission rate
OS overall survival
r/r relapsed/refractory
SCT stem-cell transplantation

1. EXECUTIVE SUMMARY

KYMRIAH is an immunotherapy. It consists of autologous T cells which are genetically modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). This Biologics Licensure Application (BLA) seeks licensure of KYMRIAH in combination with lymphodepleting chemotherapy for the treatment of pediatric and young adult patients (age 3-25 years) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study (#B2202) which enrolled 88 subjects, 68 of whom received KYMRIAH as of the data cutoff of November 23, 2016. Data from the 63 subjects who were infused with KYMRIAH manufactured in the U.S. facility form the basis for the efficacy review in this memo. The pre-specified primary efficacy endpoint was overall remission rate (ORR), defined as the proportion of patients with a best overall response (BOR) of complete remission (CR) or CR with incomplete blood count recovery (CRi), as determined by independent review committee (IRC) assessment during the 3 months after KYMRIAH administration. The overall remission rate was 82.5% (=52/63) and the lower limit of the 95% exact Clopper-Pearson confidence interval is 70.9%, which is above the pre-set null hypothesis rate of 20%. Among the 52 responders, forty subjects (63%) had a best response of CR within the first 3 months after infusion, and 12 subjects (19%) had

a best response of CRi. The median duration of response (DOR) was not yet reached after a median follow-up of 4.8 months. The estimated relapse-free rate among responders at 6 months was 75.4% (95% CI: 57.2, 86.7).

Deaths occurred in 13.6% (12/88) of enrolled subjects before KYMRIAH infusion and 16.2% (11/68) of infused subjects. Serious adverse events (SAEs) were reported in 61.4% (54/88) of subjects prior to KYMRIAH infusion and in 75% (51/68) of infused subjects. The most common serious adverse event (SAE) was Cytokine Release Syndrome (CRS) which was reported in 63.2% (43/68) of infused subjects.

Efficacy results in Study B2202 meet the study objective of demonstrating that ORR is statistically significantly greater than the pre-specified null hypothesis rate of 20%. The statistical analysis results provide evidence to support the applicant's proposed indication for KYMRIAH in this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

Acute lymphoblastic leukemia (ALL) is the malignant proliferation of lymphoid progenitor cells in the bone marrow, characterized by an excess of malignant lymphoblasts. The majority of ALL malignancies are of B-cell origin. Treatment of B-cell ALL typically consists of combination chemotherapy delivered during several phases of therapy administered over a 2- to 3-year period (first-line therapy). Relapsed B-cell ALL is treated with salvage chemotherapy, and/or stem cell transplantation (SCT, 2nd line or greater therapy).

Optimal use of anti-leukemic agents, together with the use of prognostic factors for risk-directed therapy has led to a good prognosis in pediatric and young adult ALL patients with a cure rate of greater than 80% in developed countries. According to the applicant, approximately 20% of pediatric patients will relapse, with relapsed ALL remaining one of the leading causes of death in pediatric cancer. Though most pediatric patients (>85%) with relapsed ALL will achieve a second remission, the challenge remains to maintain this second remission as most patients who relapse once will relapse again, and will ultimately succumb to their disease.

2.1 Disease or Health-Related Condition(s) Studied

The disease investigated in this BLA is relapsed/refractory B-cell acute ALL for pediatric and young adult subjects.

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

Currently available FDA approved therapies for relapsed/refractory (r/r) ALL include BLINCYTO with an ORR of 33% and CLOFAR with an ORR of 19.7%.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The first human study for this product was Study B2101J, which was part of this BLA submission (see brief information of Study B2101J in Table 2).

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

Table 1 below summarizes the Pre- and post-submission regulatory activities.

Table 1. Summary of Pre-and Post submission regulatory activities

Date	Milestone
4/22/2013	PreIND Meeting
3/03/2014	PreIND Meeting
3/04/2014	Special Protocol Assessment (SPA)
9/23/2014	IND 16130 submission
9/23/2014	Rare Disease Designation
1/31/2014	Orphan Designation: Acute Lymphoblastic Leukemia
4/7/2016	Breakthrough Therapy Designation
11/21/2016	Pre-BLA Meeting
11/23/2016	Efficacy Assessment: Data Cut-off
12/16/2016	CKYMRIAHB2202 Interim Analysis with 6 months follow-up
2/02/2017	BLA 125646 submission
3/15/2017	Office of Orphan Drug Products: request for Rare Pediatric Disease Designation Granted.
3/28/2017	Filing Letter
7/12/2017	Oncologic Drugs Advisory Committee Meeting
10/03/2017	PDUFA Action Due Date

(Source: FDA clinical reviewer)

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 proposed product KYMRIAH comes from study B2202, which is the focus of this review memo.

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

The basis of this statistical memo includes review of

- Clinical study reports and data sets submitted in the original submission in module 5,
- Efficacy update submitted in amendment 2 of BLA and its associated updated efficacy data sets, and
- BLA Addendum to 2.7.4 Summary of Clinical Safety 60-day safety update.

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the three studies that enrolled ALL subjects in the BLA submission. Results from study B2202 form the primary evidence of safety and efficacy of KYMRIAH for the BLA application. Results from studies B2101J and B2205J are supportive.

Table 2. Studies with ALL indication in the BLA submission

Study code	Study design	# of subjects enrolled	Study population
B2202 (pivotal)	single-arm, multicenter Phase II study	88	pediatric and young adult patients with r/r B-cell acute lymphoblastic leukemia
B2101J (supportive)	single-arm, single-site Phase I/II trial	55	pediatric and young adult patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma
B2205 J (supportive)	single-arm, multicenter trial Phase II	29	pediatric and young adult patients 3 to 25 years of age with r/r B-cell acute lymphoblastic leukemia

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

A meeting of the Oncologic Drugs Advisory Committee was held for the product on July 12, 2017. The following voting question was posed to the committee:
Considering the efficacy and safety results of Study B2202, is the benefit-risk profile of tisagenlecleucel favorable for treatment of pediatric and young adult patients (age 3-25 years) with relapsed (second or later relapse) or refractory (failed to achieve remission to initial induction or reinduction chemotherapy) B-cell precursor acute lymphoblastic leukemia (ALL)?

Ten committee members voted “Yes” and none voted “No”.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study B2202 is the pivotal study that constitutes the primary evidence of safety and efficacy of KYMRIAH in the treatment of pediatric and young adult patients with relapsed/refractory (r/r) B-cell ALL for the BLA submission.

6.1.1 Objectives

The objectives of study B2202 were:
Primary objective
Evaluate the efficacy of KYMRIAH therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after KYMRIAH administration, which includes complete remission (CR) and CR with incomplete blood count recovery (CRi) as determined by Independent Review Committee (IRC) assessment.

Key secondary objectives

- Evaluate the efficacy of KYMRIAH therapy from US manufacturing facility as measured by ORR during the 3 months after KYMRIAH administration, which includes CR and CRi as determined by IRC assessment.
- Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a minimal residual disease (MRD) negative bone marrow by IRC using flow cytometry among all patients who received KYMRIAH from all manufacturing facilities.
- Evaluate the percentage of patients who achieved a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive KYMRIAH from US manufacturing facility.

The study is currently on-going. At the data cutoff of November 23, 2016, 63 of the infused subjects were treated with products manufactured at the U.S. facility, and only 5 were treated with products manufactured at the German facility. The 5 subjects treated with products manufactured at the German site had limited follow-up data (follow-up time ranging from 8 to 63 days). As a result, the efficacy review in this memo will only include the 63 subjects treated with U.S. facility manufactured products.

6.1.2 Design Overview

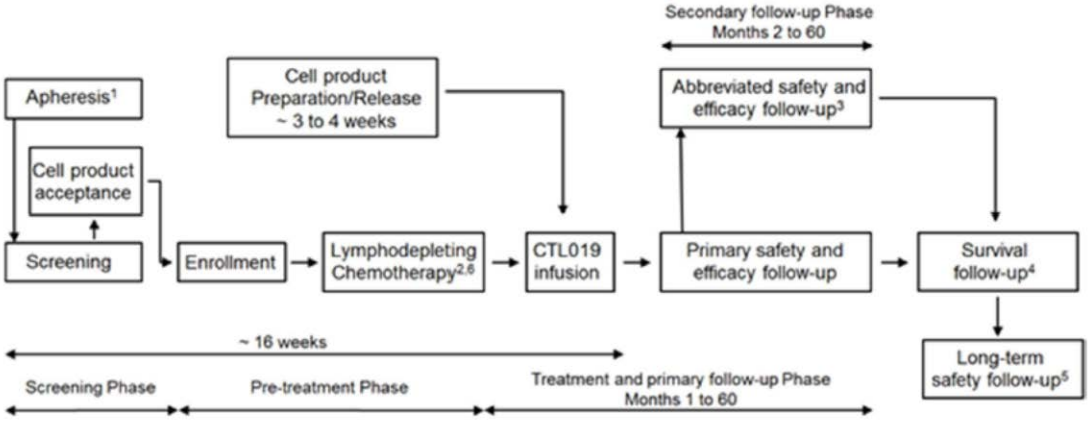
This was a single-arm, multi-center, Phase II study to determine the efficacy and safety of KYMRIAH in pediatric and young adult patients with r/r B-cell ALL. Design of the study protocol had a SPA concurrence on March 4, 2014.

The study had several sequential periods for all patients as follows: Screening, Pre-Treatment (cell product preparation and lymphodepleting (LD) chemotherapy), Treatment and Primary Follow-up, Secondary Follow-up (if applicable), and Survival

Follow-up. The total duration of the study is 5 years. After KYMRIAH infusion, efficacy was assessed monthly for the first 6 months, and then would be assessed quarterly up to 2 years and semi-annually afterwards up to 5 years, or until patient relapse.

After KYMRIAH infusion, patients entered the primary follow-up period. Patients may discontinue from primary follow-up due to reasons such as treatment failure, relapse after remission, stem-cell transplant (SCT) while in remission or voluntary withdrawal. Patients who discontinued the primary follow-up period before Month 60 continued to be followed in the secondary follow-up period in order to collect health authority requested data (e.g. delayed adverse events (AEs)) as well as survival up to 5 years after KYMRIAH infusion. For patients who discontinued from primary follow-up while in remission, relapse status would be obtained in the secondary follow-up until first relapse (if applicable). Figure 1 below gives an overview of the study design.

Figure 1.Study design



[1] Performed prior to study entry.
[2] As indicated per protocol.
[3] Only for patients who drop out of the primary Follow-up before Month 60
[4] Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term Follow-up.
[5] Long term safety Follow-up conducted per health authority guidance under a separate protocol.
[6] To be completed 2 to 14 days prior to CTL019 infusion.

(Source: Original BLA 125646/0; Clinical Study Report Section 9 Figure 9-1, p.61)

6.1.3 Population

The study population included pediatric and young adult patients with B-cell ALL who were chemo-refractory, relapsed after allogeneic SCT, or were otherwise ineligible for allogeneic SCT.

Other main inclusion criteria were:

- Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening
- Life expectancy >12 weeks
- Adequate organ function

- Karnofsky (age ≥ 16 years) or Lansky (age <16 years) performance status ≥ 50 at screening
- For each patient, the apheresis product of non-mobilized cells was received and accepted by the manufacturing site

6.1.4 Study Treatments or Agents Mandated by the Protocol

KYMRIAH was administered as a single intravenous infusion at the dose of 2.0 to 5.0 $x10^6$ transduced viable T cells per kg body weight (for patients ≤ 50 kg) or 1.0 to 2.5 x 10^8 transduced viable T cells (for patients > 50 kg)

6.1.6 Sites and Centers

Subjects were enrolled and treated in 25 centers across US, EU, Canada, Australia, and Japan. In the U.S., 13 centers enrolled 50 subjects. Canada had 2 centers and enrolled 6 subjects. Europe had 8 centers and enrolled 28 subjects. Japan had one center and enrolled 3 subjects. Australia had one center and enrolled one subject.

Five subjects in Europe were treated with products manufactured at a German facility, all the other subjects, including all U.S. subjects, were treated with U.S. manufactured products.

6.1.7 Surveillance/Monitoring

According to the applicant it was expected that adverse events (AEs) would occur frequently in this population based on the underlying advanced hematologic malignancy and that these can be serious adverse events (SAEs). Therefore, the applicant stated that there was no specific occurrence of SAEs that define a stopping rule, but the review of SAEs will form the basis for potential early stopping of the study. Only unexpected SAEs that were related to the KYMRIAH transduced cells may trigger early stopping of the trial The review of these adverse events, and any decision to prematurely stop patient enrollment, was determined by the Data Monitoring Committee (DMC) and reviewed by the IRB at the site level.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint
The primary endpoint was the ORR which was defined as the proportion of patients who achieved a BOR of CR or CRi, as determined by IRC assessment during the 3 months after KYMRIAH administration.

A full response evaluation, including assessments of peripheral blood, bone marrow, central nervous system (CNS) symptoms, physical exam, and cerebrospinal fluid (CSF) assessment by lumbar puncture (LP), is required at the first time a CR or CRi is demonstrated.
In order for the best overall response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28

days) after the initial achievement of CR or CRi. If additional assessments of bone marrow and/or CSF are performed in the same evaluation, they will also need to show remission status. The analysis of the primary efficacy endpoint will be performed by testing whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that ORR within 3 months is greater than 20% at overall one-sided 2.5% level of significance, i.e.,
H0: $p \leqslant 0.2$ vs. Ha: $p > 0.2$.

Key secondary endpoint
The key secondary endpoint of the study is the percentage of patients who achieved a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry during the 3 months after KYMRIAH administration among all patients who receive KYMRIAH from US manufacturing facility.

Hypothesis testing will be performed to test whether the above rate is less than or equal to 15% against the alternative hypothesis that it is greater than 15% i.e.,
H0: $p \leqslant 0.15$ vs. Ha: $p > 0.15$.

This hypothesis testing will only be performed if the primary efficacy endpoint ORR reaches statistical significance, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme.

The study protocol also included several other secondary endpoints for supportive purposes.

a. a. Duration of remission (DOR) is the duration from the date when the response criteria of CR or CRi are first met to the date of relapse or death due to underlying cancer. Percentage of patients who achieve CR or CRi at Month 6 without SCT
b. Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment
c. Relapse free survival (RFS) which is measured by the time from achievement of CR or CRi whatever occurs first to relapse or death due to any cause during CR or CRi. Event free survival (EFS) is the time from date of first KYMRIAH infusion to the earliest of the following:
    - Death from any cause after remission
    - Relapse
    - Treatment failure is defined as no response in the study and discontinuation from the study due to any of the following reasons, death, adverse event, lack of efficacy, progressive disease or new anticancer therapy
d. Overall survival (OS) is the time from date of first KYMRIAH infusion to the date of death due to any reason.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypotheses:
The analysis of the primary efficacy endpoint will be performed by testing whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that it is greater than 20% at overall one-sided 2.5% level of significance, i.e.,
H0: $p \leqslant 0.2$ vs. Ha: $p > 0.2$.

The analysis of the key secondary efficacy endpoint will be performed by testing whether the percentage of subjects who achieve a BOR of CR or CRi with a MRD negative bone marrow is less than or equal to 15% against the alternative hypothesis that it is greater than 15% at overall one-sided 2.5% level of significance, i.e.,
H0: $p \leqslant 0.15$ vs. Ha: $p > 0.15$.

Analysis populations
Screened Set
The Screened Set comprises all patients who have signed informed consent/assent and screened in the study.

Enrolled Set
The Enrolled Set comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility.

Full Analysis Set
The Full Analysis Set (FAS) comprises all patients who received infusion of KYMRIAH.

Interim Efficacy Analysis Set (IEAS)
At the time of interim analysis, the Interim Efficacy Analysis Set (IEAS) comprises the first 50 patients who receive KYMRIAH infusion.
(Reviewer's comment: the 50 subjects was the planned sample size of the original protocol and there was no interim analysis in the original protocol. As the applicant expanded the study and enrolled more subjects (protocol amendment #4), the original final analysis is now an interim analysis.)

Efficacy analysis set (EAS)
The Efficacy Analysis Set is the subset of the FAS subjects treated with KYMRIAH manufactured from the U.S. facility.

Safety Set
The Safety Set comprises all patients who received infusion of KYMRIAH.

Per-Protocol Set
The Per-Protocol Set (PPS) consists of a subset of the patients in the IEAS or FAS (at interim and final analysis respectively) who are compliant with major requirements of the clinical study protocol (CSP).
Major protocol deviations leading to exclusion from the PPS include:

- No diagnosis of ALL at baseline;

- Prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens;
- Missing or incomplete documentation of disease;

In addition, patients who received a dose less than the minimum target dose of 2×10^6/kg (for patients $\leqslant$ 50 kg) or 1 x 10^8 (for patients > 50 kg) KYMRIAH transduced viable T cells will also be excluded.

Statistical methods

Primary endpoint and the key secondary endpoint

The primary efficacy endpoint, ORR within 3 months, will be analyzed at the interim look and final look of a group sequential design. The ORR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets. *(Reviewer's comment: Since the study doesn't plan to stop to claim efficacy at the interim, it is not needed to spend α at the interim. In this review memo, the interim analysis is ignored and the final analysis will use the whole two-sided α of 0.05.)*

The proposed key secondary endpoint, percentage of subjects who achieve a BOR of CR or CRi with a MRD negative bone marrow, will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with a coverage level according to the above alpha spending function.

Other secondary endpoints

a. Duration of remission (DOR)

Duration of remission (DOR) is defined as the duration from the date when the response criteria of CR or CRi is first met to the date of relapse or death due to underlying cancer. DOR will be assessed only in patients with the best overall response of CR or CRi ("responders"). In case a patient does not have relapse or death due to ALL prior to data cutoff, DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessments

If among responders death occurs due to reasons other than ALL, a competing risk analysis will be conducted and the estimated percentage of relapsed patients (at 6 months, 12 months, etc.) will be presented with 95% confidence intervals using the cumulative incidence function (CIF). In the absence of non-relapse mortality, the Kaplan-Meier method will be used and the median DOR along with 95% confidence intervals will be presented.

In either case, the primary analysis will censor subjects who receive SCT while in response to KYMRIAH at date of the transplant. In an exploratory analysis, the date of

relapse or death (if due to the underlying cancer) after SCT will be used for DOR calculation.

b. Percentage of patients who achieve CR or CRi at Month 6 without SCT

The percentage of patients who achieve CR or CRi at Month 6 without SCT (post KYMRIAH infusion) between KYMRIAH infusion and Month 6 response assessment, among all patients in the FAS, will be summarized along with exact 95% confidence interval. In addition, the percentage among patients who achieved CR or CRi will also be summarized.

c. Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment

The percentage of patients who achieve CR or CRi and then proceed to SCT while in remission by the time of Month 6, among all patients in the FAS, will be summarized along with exact 95% CI. In addition, the percentage will also be summarized among all patients who achieved CR or CRi.

d. Relapse free survival (RFS)

RFS will be assessed only in patients with the best overall response of CR or CRi. In case a patient does not have relapse or death due to any cause prior to data cutoff, RFS will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessments

In the primary analysis of RFS, patients who proceed to SCT while in response to KYMRIAH infusion will be censored at the time of SCT. In addition, a sensitivity analysis of RFS will be performed without censoring SCT.

The distribution function of RFS will be estimated using the Kaplan-Meier method. The median RFS along with 95% confidence intervals will be presented.

e. Event free survival (EFS)

For analysis of EFS, in case of treatment failure, the event date will be set to study Day 1. In case a patient does not have relapse, death due to any cause or treatment failure (e.g. discontinuation as a result of withdrawal of consent, lost to follow-up, protocol violation or administrative problems) prior to data cutoff, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event (except for SCT). The censoring reason could be

- Ongoing without event

- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessment

In the primary analysis of EFS, patients who proceed to SCT after KYMRIAH infusion will be censored at the time of SCT. In addition, a sensitivity analysis of EFS will be performed without censoring SCT. The distribution function of EFS will be estimated using the Kaplan-Meier method. The median EFS along with 95% confidence intervals will be presented.

f. Overall survival (OS)

In case a patient is alive at the date of last contact on or before data cutoff, OS is censored at the date of last contact. No censoring will be done in case of SCT. The distribution function of OS will be estimated using the Kaplan Meier method. The median OS along with 95% confidence intervals will be presented.

Multiplicity

The primary efficacy endpoint will be analyzed at the interim look and final look of a group sequential design. The study protocol proposed to control the type I error probability using a Lan-DeMets (O'Brien-Fleming) alpha spending function at one-sided 2.5% level of significance.

The hypothesis testing of the key secondary endpoint will only be performed if the hypothesis of the primary endpoint is rejected, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. In testing the key secondary endpoint, the type I error probability will also be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

Sample size

Based on the null hypothesis of ORR $\leq$ 20% and alternative hypothesis of ORR >20%, up to 76 patients in the FAS will provide more than 95% power to demonstrate a statistical significance at one-sided 2.5% level of significance, if the underlying ORR is 45%.

Accounting for the patients to assess KYMRIAH manufactured from the Fraunhofer Institute, and assuming 20% to 25% enrolled patients will not be infused due to reasons such as KYMRIAH product manufacturing issues, worsening of patient's condition, etc., approximately 95 patients were planned for the study.

Interim analyses

An interim analysis will be performed when the first 50 patients who receive KYMRIAH have completed 3 months from study day 1 infusion or discontinued earlier. The final analysis of the primary endpoint will be performed after all patients infused with

KYMRIAH have completed 3 months follow-up from study day 1 infusion or discontinued earlier.

Subgroup analysis

Subgroup analyses will be performed on the following based on the patient's baseline status:

- Age: <10 years, ⩾10 years to <18 years, ⩾18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Prior response status: Primary refractory, Chemo-refractory, Relapsed disease
- Prior SCT therapy: Yes, No
- Eligibility for SCT: Eligible for SCT, ineligible for SCT
- Baseline bone marrow tumor burden: Low (defined as either morphologic or MRD result is <50% and neither is ⩾50%), High (defined as either morphologic or MRD result is ⩾50%)
- Baseline extramedullary disease presence: Yes, No
- Philadelphia chromosome/BCR-ABL: Positive, Negative
- Mixed-Lineage Leukemia (MLL) rearrangement: Yes, No
- Hypoploidy: Yes, No
- BCR-ABL1-like: Yes, No
- Complex Karyotypes (⩾5 unrelated abnormalities): Yes, No
- Down syndrome: Yes, No

Missing data

Patients in the study who are of unknown clinical response will be treated as non-responders. If there is evidence of relapse, the overall response will be assessed as "relapsed disease" with the relapsed component alone.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 3 shows the number of subjects in the analysis sets. A total of 107 subjects were screened and 88 of them were enrolled in the study. Among enrolled subjects, a total of 68 subjects constitute the FAS (subject who received KYMRIAH). As described in section 6.1.1, 63 subjects in the FAS were treated with KYMRIAH manufactured from the U.S. facility site and therefore form the efficacy analysis set (EAS) for this memo. The other 5 subjects in the FAS were treated with KYMRIAH manufactured from the German facility site.

Table 3. Analysis sets

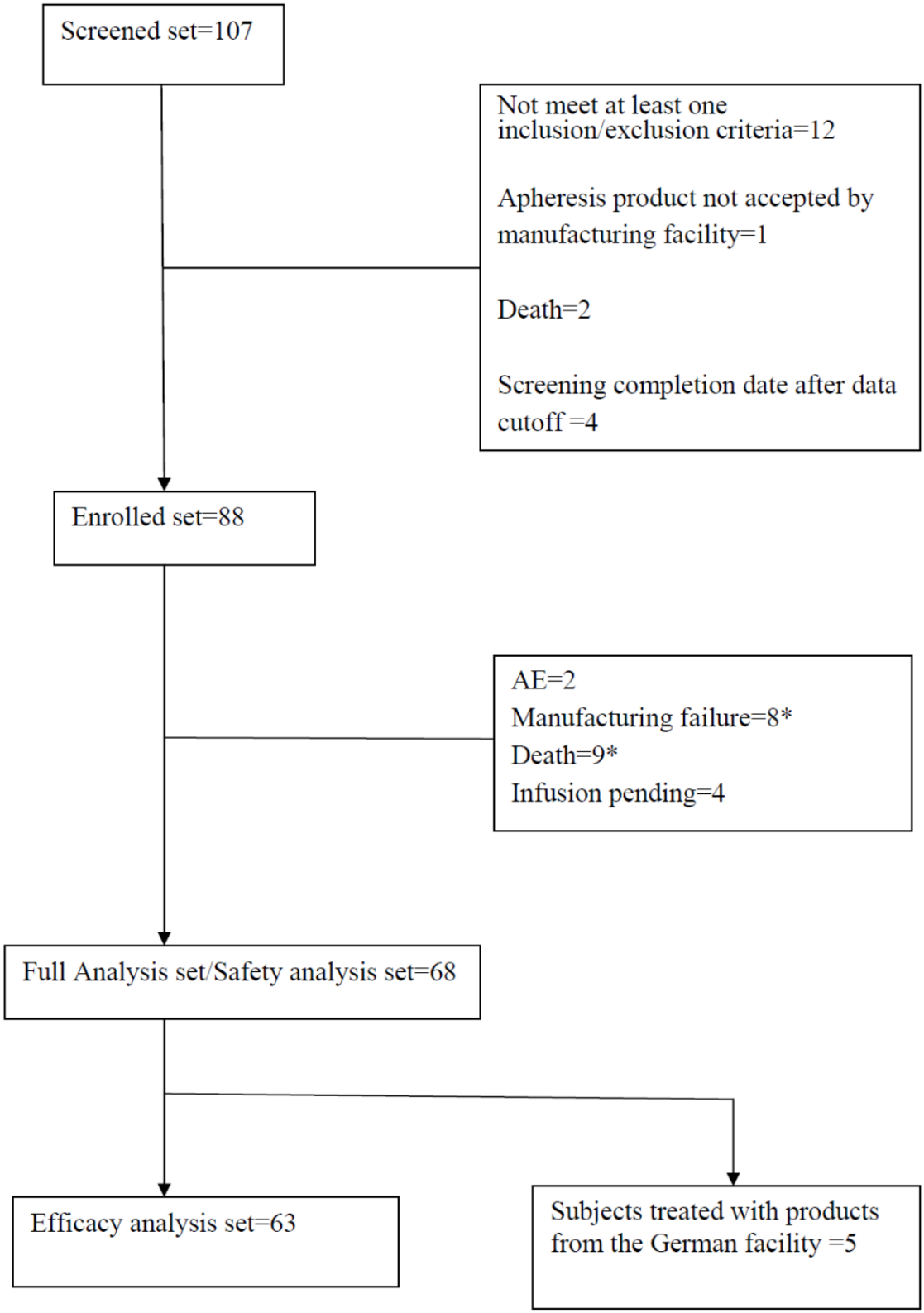
Analysis Set	Number of subjects N (%)
Screened Set	107 (100%)

Enrolled Set	88 (82%)
Full Analysis Set /Safety Set	68 (64%)

(Source: FDA statistical reviewer's analysis)

Figure 2 shows the detailed disposition information for each of the analysis set.

Figure 2. Subjects disposition



*three(3) subjects counted twice, they had manufacture failure and they died too
(Source: FDA statistical and clinical reviewer's joint analysis)

6.1.10.1.1 Demographics
Table 4 shows the demographic information for subjects in the Enrolled Set and the Full Analysis Set. Subjects' demographics in the two analysis sets were similar.

Table 4. Demographics for the Enrolled Set and FAS

	Enrolled Set N=88	Full Analysis Set N=68
Age		
Mean (SD)	12.1 (5.4)	12.2 (5.3)
Median (Min, Max)	11.5 (3, 27)	12 (3, 23)
Age category		
<10	37 (42%)	28 (41%)
>=10 to <18	35 (40%)	28 (41%)
>=18	16 (18%)	12 (18%)
Sex		
Male	48 (55%)	38 (56%)
Race		
White	65 (74%)	51(75%)
Asian	10 (11%)	6 (9%)
African American	1 (1%)	1 (1%)
Other	12 (14%)	10 (15%)
Ethnicity		
Hispanic or Latino	17 (19%)	14 (21%)
Other	71 (81%)	54 (79%)

(Source: FDA statistical reviewer's analysis)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Table 5 shows the baseline characteristics for subjects in the Enrolled Set and the Full Analysis Set. There are no outstanding differences with respect to subject baseline characteristics between the two analysis sets.

Table 5. Baseline characteristics for the Enrolled Set and FAS

	Enrolled Set N=88	Full Analysis Set N=68
Age at initial diagnosis		
Mean (sd)	7.8 (5.2)	7.6 (5.0)
Median (min, max)	7 (0,21)	7 (0,21)
Age group at initial diagnosis		
<10	58 (66%)	47 (69%)
>=10	30 (34%)	21 (31%)

Response status at study entry		
Chemo refractory	9 (10%)	8 (12%)
Primary refractory	8 (9%)	6 (9%)
Relapse disease	71 (81%)	54 (79%)
Performance Status at Baseline		
Mean(sd)	87 (13.5)	87 (13.5)
Median(min, max)	90 (50, 100)	90 (50, 100)
Number of Prior HSCT performed		
0	36 (41%)	28 (41%)
1	45 (51%)	35 (51%)
2	7 (8%)	5 (8%)
Number of Previous Lines of Therapies		
Median (min, max)	3 (1,8)	3 (1,8)
Number of Previous Complete Remissions		
Median (min, max)	2(0,6)	2 (0, 6)

(Source: FDA statistical reviewer's analysis)

6.1.10.1.3 Subject Disposition

For the 68 subjects in the full analysis set, 36 were still in the primary follow-up period at the time of analysis data cutoff, and 32 were not. Among this group of 32 subjects, five died, 15 entered the secondary follow-up period and 12 did not enter secondary follow-up but only agreed to survival follow-up. The reasons for discontinuation from the primary follow-up are the following:

- 5 deaths
- 14 lack of efficacy
- 11 new therapy for study indication
- 2 subject/guardian decision

For the 15 subjects who entered the secondary follow-up period, 2 subjects died and the remaining 13 subjects were in the secondary follow-up at the data cutoff.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

In the efficacy analysis set (EAS) of 63 subjects, 52 subjects (82.5%) had a best overall response of CR or CRi, as determined by IRC. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR is 70.9%, which is well above the null hypothesis rate of 20%. Among the 52 responders, 40 subjects (63%) had a best response of CR

within the first 3 months after infusion, and 12 subjects (19%) had a best response of CRi.

To assess robustness of study results, analysis results of the primary endpoint ORR are presented in Table 6 for the Enrolled Set, the Modified Enrolled Set and the Full Analysis Set. The modified enrolled set is the set of enrolled subjects who were intended to be treated with KYMRIAH manufactured at the U.S. facility. These were subjects who were enrolled and their apheresis products were accepted at the U.S. facility. The lower limits of the 95% exact Clopper-Pearson confidence intervals for ORR are all well above the null hypothesis rate of 20% regardless of analysis set.

Table 6. ORR Results for the Enrolled Set, Modified Enrolled Set and Efficacy Analysis Set

	Enrolled Set (n=88)	Modified Enrolled Set* (n=78)	Efficacy analysis Set (n=63)
ORR (95% CI)	59.1% (48.1, 69.5)	66.7% (55.1, 76.9)	82.5% (70.9, 91.0)
CR	45.5%	54.8%	63%
CRi	13.6%	16.4%	19%

* subjects who were enrolled and their apheresis products were accepted at the U.S. facility.
(Source: FDA statistical reviewer and clinical reviewer)

The applicant reported that IRC and investigator results are 100% concordant.

6.1.11.2 Analyses of Secondary Endpoints

Key secondary endpoint: Remission with MRD negative bone marrow
All 52 subjects (100%) who achieved a BOR of CR or CRi had negative MRD when the status was initially achieved. Thus the results for the key secondary endpoint are the same as those for the primary endpoint. Based on efficacy analysis set, the lower limit of the 95% exact Clopper-Pearson confidence interval for remission rate with MRD negative bone marrow is 70.9%, which is above the pre-set null hypothesis rate of 15%.

Other secondary endpoints:
Duration of remission (DOR)
Among the 52 subjects who achieved a BOR of CR or CRi, 13 had relapsed disease (and 3 died afterwards). The applicant reported 11 cases of relapsed disease, and the other two relapse were censored because the date of relapse was after new cancer treatment was initiated.

Twenty-nine subjects were still in remission at the last assessment before the data cutoff.

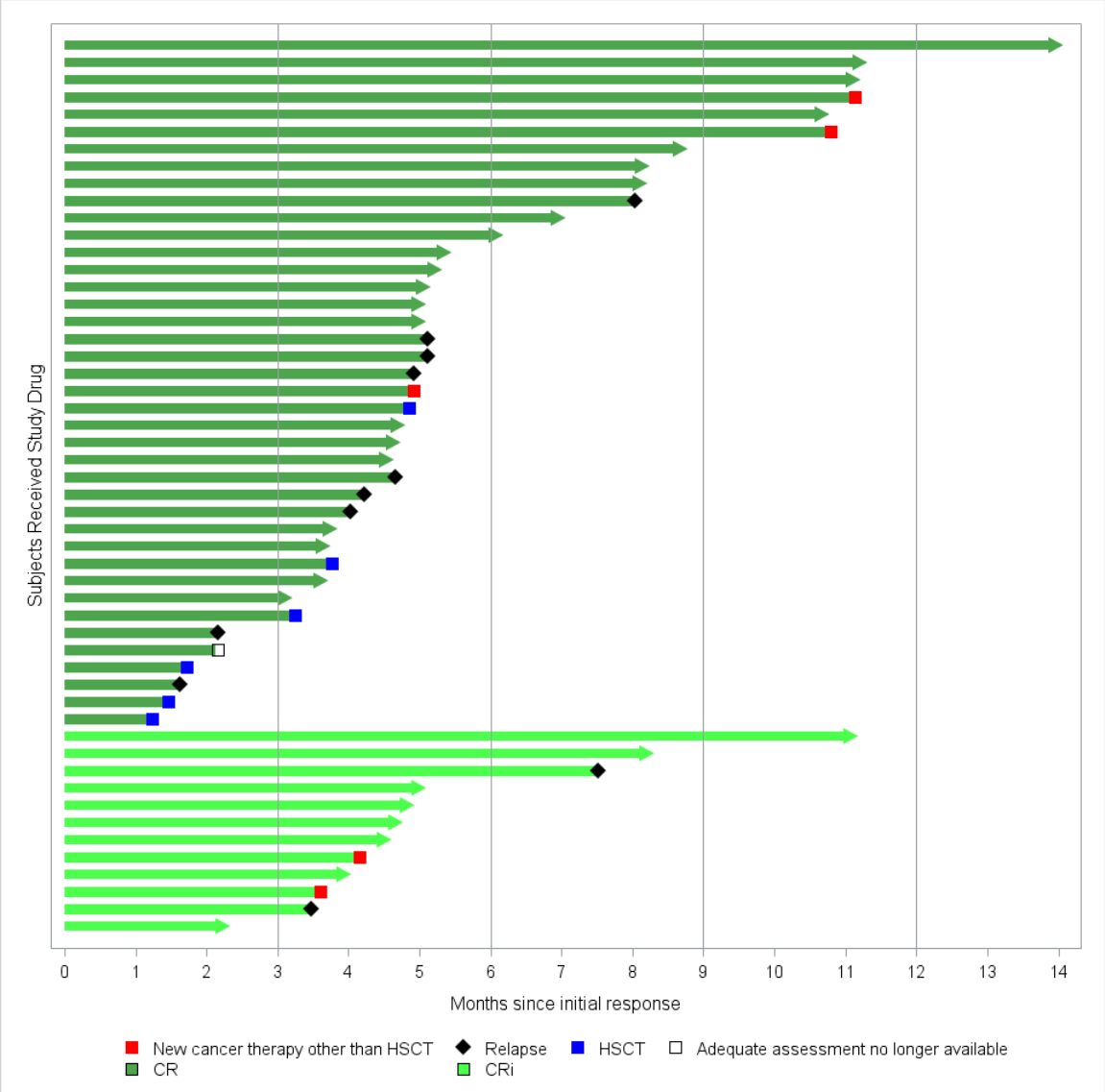
Twelve subjects were not in remission and were censored for DOR as follows: 6 patients for SCT, 5 patients for new cancer therapy, and 1 patient for adequate assessment no longer available.

Four deaths occurred among responders and three occurred after disease relapse; the remaining death occurred after new cancer therapy. The DOR was censored at the last adequate disease assessment before the initiation of the new cancer therapy, therefore the death was not a competing risk for relapse. With the absence of non-relapse mortality, competing risk analysis was not conducted. Instead, the Kaplan-Meier analysis was used to analyze DOR.

The median follow-up time for DOR was 4.8 months (min=1.2, max= 14.1). The median DOR was not reached. The estimated relapse free rate was 75.4% (95% CI: 57.2, 86.7) among responders at 6 months, and 63.8% (95% CI: 41.5, 79.4) at 12 months.

Figure 3 shows the swimmer plot of DOR that gives detailed status for each individual subject.

Figure 3. Swimmer plot of duration of response (DOR)



(Source: FDA statistical reviewer's analysis)

Relapse-free survival (RFS)
In the absence of competing risk, the RFS result is the same as the DOR shown previously.

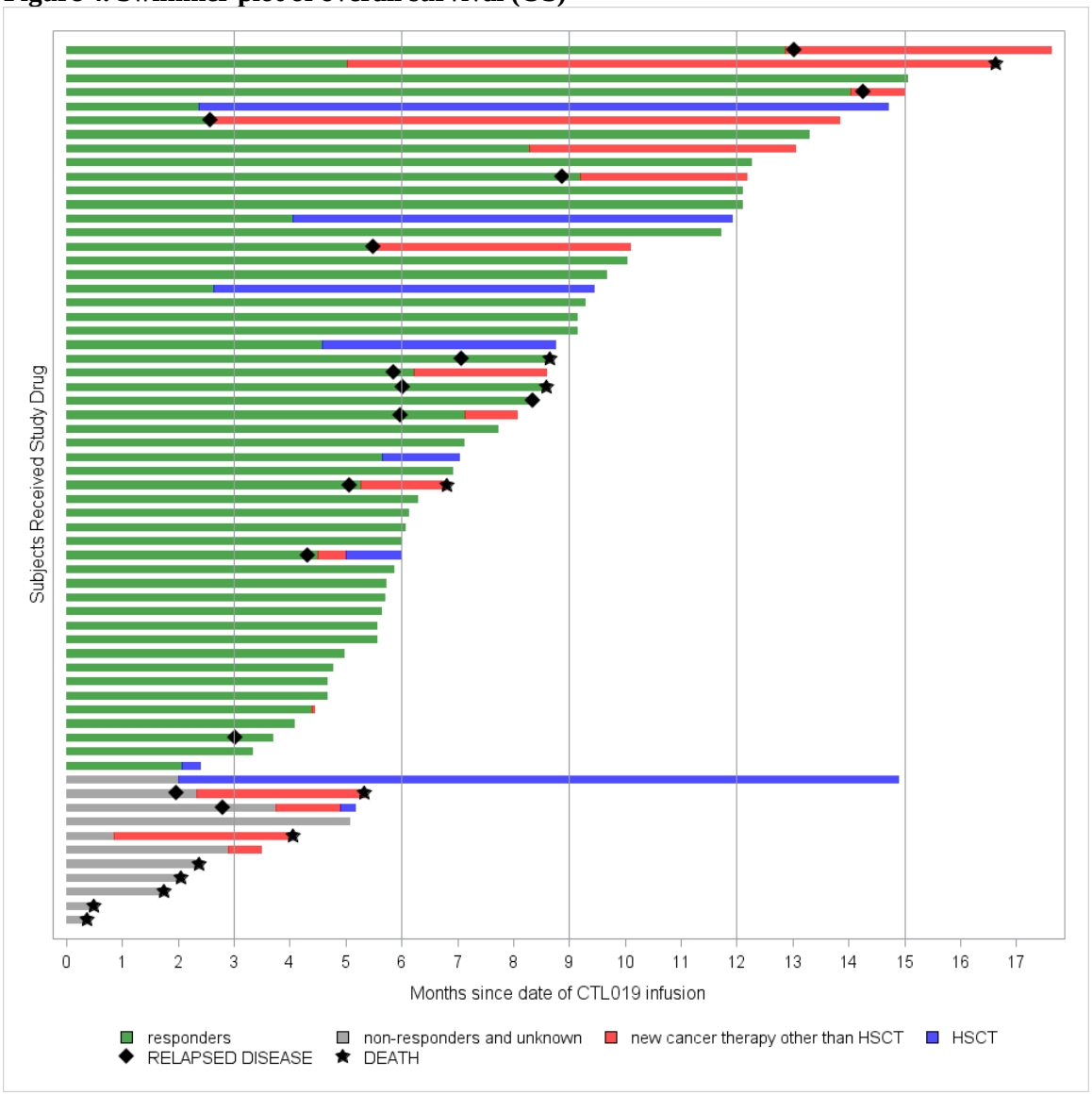
Event free survival (EFS)
The median follow-up for EFS was 5.6 months (min=1 day, max=15.1 months). Approximately 31.7% (= 20/63) had an event. The median EFS had not yet been reached at the time of data cutoff. The estimated event-free survival rate at 6 months was 69.6% (95% CI: 54.4, 80.6), and at 12 months it was 53.3% (95% CI: 34.8, 68.7).

Overall survival (OS)
A total of 11 of the 63 (17.5%) of the subjects who received KYMRIAH infusion died.

The median follow-up time for OS was 6.9 months (min=9 days, max=17.7 months). Median OS was 16.6 months (95% CI: 16.6, NE). The estimated survival rate at 6 months was 88.4% (95% CI: 77.0, 94.3), and at 12 months it was 78.9% (95% CI: 63.0, 88.6).

Figure 4 shows the swimmer plot of OS in the EAS, giving detailed OS status of each individual subject.

Figure 4. Swimmer plot of overall survival (OS)



(Source: FDA statistical reviewer's analysis)

Clinical response with/without SCT by Month 6

Among the 52 subjects achieved CR or CRi, 7 (13.5%) proceeded to receive SCT, and 45 (86.5%) subjects did not receive SCT. Among the 7 subjects received SCT, 1 subject had relapsed disease and received other anticancer treatment, then proceeded to SCT. The other 6 had no relapsed disease by the data cutoff.

For the 45 subjects who achieved CR or CRi and did not receive SCT, 12 had relapsed disease (2 relapsed after new cancer treatment) and 8 of them relapsed within 183 days of

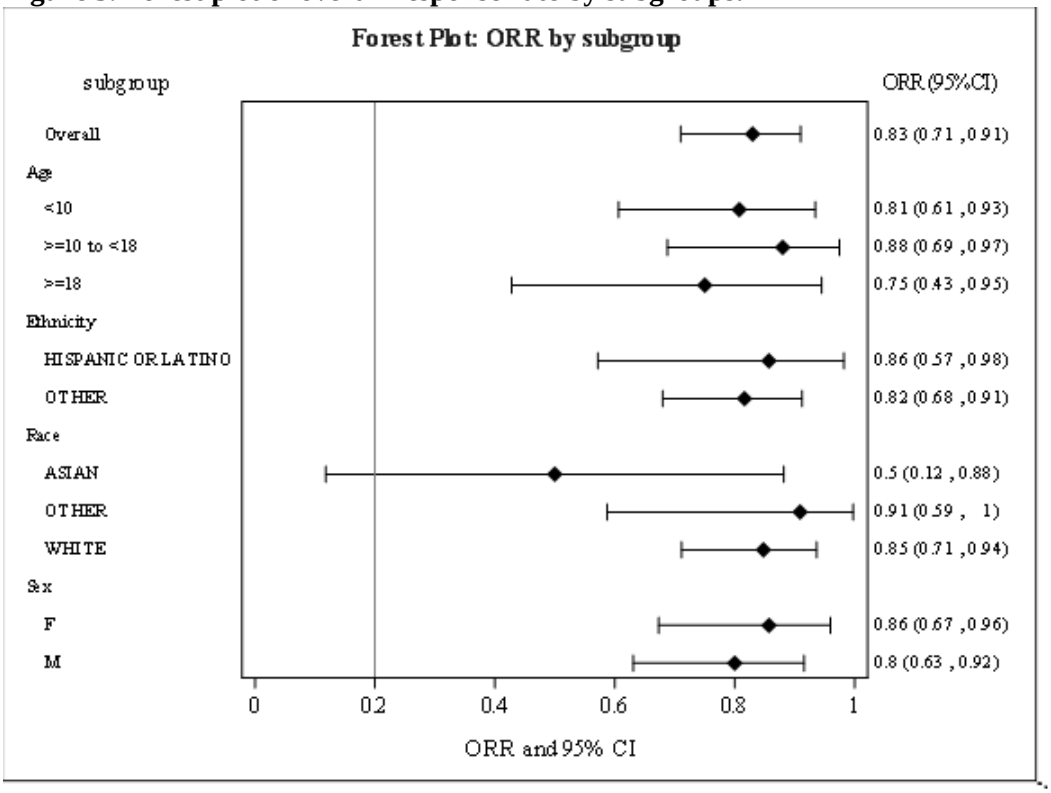
CLT19 infusion. Three subjects received new cancer treatment and one subject was lost to follow-up. A total of 29 subjects were still in remission at the last assessment before the data cutoff.

Two subjects received SCT without achieving CR or CRi. One had relapsed disease and received other anticancer treatment and then proceeded to SCT. The other did not have any disease assessment beyond day 28. All SCT occurred within 6 months of CTL 19 infusion.

6.1.11.3 Subpopulation Analyses

Figure 5 shows the forest plot of overall remission rate (ORR) by age group, ethnicity, race and sex. Results of ORR seem to be generally consistent among subgroups.

Figure 5. Forest plot of overall response rate by subgroups.



(Source: FDA statistical reviewer's analysis)

Asian and White combined counted for 83% of the efficacy analysis set. Because the other race categories are small (1 AMERICAN INDIAN OR ALASKA NATIVE and 1 BLACK OR AFRICAN AMERICAN, 6 "other" and 3 unknown), no additional subgroup analysis was carried out for other racial groups besides Asian and White.

Table 7 shows subgroup analysis of ORR by country. It appears that Japan and Canada had a lower ORR than the other countries. However, the number of treated subjects in the two countries was too small to make any conclusion.

Table 7. Subgroup analysis of ORR by country

Country	# of subjects in EAS (total=63) n (%)	ORR # of responder (%)
Australia	1(2%)	1 (100%)
Canada	5(8%)	2 (40%)
Japan	2(3%)	1 (50%)
U.S.	39(62%)	33 (84.6%)
European countries	16(25%)	15 (94%)
Overall	63 (100%)	82.5%

Table 8 shows subgroup analysis of ORR by study site for U.S. treated subjects. It appears that four sites had lower ORR than the other sites, however, the number of subjects treated at these sites was too small to make any conclusion.

Table 8. Subgroup analysis of ORR for U.S. treated subjects by study site

Study Site	# of subjects treated in the U.S. (total=39) n (%)	ORR # of responders (%)
1401	10 (26%)	9 (90%)
1404	2 (5%)	1 (50%)
1405	5 (13%)	3 (60%)
1406	3 (8%)	3 (100%)
1407	3 (8%)	3 (100%)
1408	2 (5%)	2 (100%)
1409	2 (5%)	1 (50%)
1410	3 (8%)	2 (67%)
1411	4 (10%)	4 (100%)
1412	2 (5%)	2 (100%)
1413	3 (8%)	3 (100%)
U.S. overall	39 (100%)	33 (84.6%)

6.1.11.4 Dropouts and/or Discontinuations

Table 9 summarizes subjects' dropout and discontinuations.

Table 9. Subjects disposition

Enrolled in the study	88 (100%)
Discontinued prior to KYMRIAH infusion	16 (18%)
Manufacture failure	8 *(9%)
Death	9 *(10%)

Adverse event	2 (2%)
Infusion pending	4 (5%)
Infused	68 (77%)
Primary follow-up on-going	36 (41%)
Secondary follow-up on-going	13 (15%)
Survival follow-up on-going	12 (14%)
Death	7 (8%)

*three(3) subjects counted twice, they had manufacture failure and they died too

6.1.12 Safety Analyses

This section summarizes safety results of Study B2202.

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data for study B2202.

6.1.12.3 Deaths

The applicant reported the following deaths (Table 10). Among the 88 enrolled subjects, 12 subjects (13.6%) died before KYMRIAH infusion. Among the 68 subjects infused with KYMRIAH, 11 subjects (16.2%) died due.

Table 10. Deaths reported

Patients enrolled	**N=88 (%)**
Any time before KYMRIAH infusion	12 (13.6%)
Death Due to ALL	6 (6.8%)
Death Due to Other reasons	6 (6.8%)
Patients infused	**N=68 (%)**
Any time post KYMRIAH infusion	11 (16.2%)
Death Due to ALL	7 (10.3%)
Death Due to Other reasons	4 (5.9%)

(Source: adapted Addendum to 2.7.4 Summary of Clinical Safety 60-day safety update Table 2-7)

6.1.12.4 Nonfatal Serious Adverse Events

The applicant reported that prior to KYMRIAH infusion, among the 88 enrolled subjects, 54 subjects (61.4%) experienced SAEs.
Among the 68 infused subjects, SAEs were reported in 75.0% of infused subjects; primarily attributed to the proportion of subjects with CRS (63.2%).
Table 11 summarizes SAEs post KYMRIAH infusion as reported by the applicant.

Table 11. Serious adverse events post KYMRIAH infusion

Preferred Term	All Grades* N (%)	Grade 3 N(%)	Grade 4 N (%)
Patients with at least one SAE	51 (75.0)	20 (29.4)	27 (39.7)
Cytokine release syndrome	43 (63.2)	13 (19.1)	18 (26.5)
Febrile neutropenia	14 (20.6)	13 (19.1)	1 (1.5)
Hypotension	8 (11.8)	1 (1.5)	7 (10.3)
Pyrexia	5 (7.4)	1 (1.5)	0
Acute kidney injury	5 (7.4)	2 (2.9)	3 (4.4)
Hypoxia	4 (5.9)	2 (2.9)	2 (2.9)
Cardiac arrest	3 (4.4)	0	3 (4.4)
Respiratory failure	3 (4.4)	0	3 (4.4)
Upper respiratory tract infection	3 (4.4)	3 (4.4)	0

*This column includes SAEs from Grade 1 to Grade 4s.
(Source: adapted Addendum to 2.7.4 Summary of Clinical Safety 60-day safety update Table 2-9)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 12 summarizes the AESI post KYMRIAH infusion as reported by the applicant.

Table 12. Adverse events of special interest (AESI) within 8 weeks post KYMRIAH infusion, regardless of study drug relationship, by group term and maximum grade

Group term	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least one SAE	62 (91.2)	23 (33.8)	28 (41.2)
Cytokine release syndrome	53 (77.9)	14 (20.6)	18 (26.5)
Febrile neutropenia	25 (36.8)	23 (33.8)	2 (2.9)
Hematopoietic cytopenias not resolved by day 28	25 (36.8)	10 (14.7)	12 (17.6)
Infections	29 (42.6)	16 (23.5)	2 (2.9)
Transient neuropsychiatric events	30 (44.1)	10 (14.7)	0
Tumor Lysis Syndrome	3 (4.4)	3 (4.4)	0

*This column includes SAEs from Grade 1 to Grade 4s.
(Source: adapted Addendum to 2.7.4 Summary of Clinical Safety 60-day safety update Table 5-2)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support this application is a Phase II, single-arm, multicenter study which enrolled 88 subjects, sixty-eight (68) of whom received KYMRIAH as of the data cutoff of November 23, 2016. Sixty-three (63) subjects were infused with KYMRIAH manufactured in the U.S. facility, forming the basis for the efficacy review in this memo. The pre-specified primary efficacy endpoint was ORR, defined as the proportion of patients with a BOR of CR or CRi, as determined by IRC assessment during the 3 months after KYMRIAH administration. The ORR was 82.5% (=52/63) and the lower limit of the 95% exact Clopper-Pearson confidence interval is 70.9%, which is above the pre-set null hypothesis rate of 20%. Forty subjects (63%) had a best response of CR within the first 3 months after infusion, and 12 subjects (19%) had a best response of CRi. Among the 52 responders, the median DOR was not yet reached with the median follow-up of 4.8 months. The estimated relapse-free rate among responders at Month 6 was 75.4% (95% CI: 57.2, 86.7).

Deaths occurred in 13.6% (= 12/88) of enrolled subjects prior to KYMRIAH infusion and in 16.2% (= 11/68) of subjects post-infusion. Serious adverse events (SAEs) were reported in 61.4% of subjects (= 54/88) prior to KYMRIAH infusion and in 75% (= 51/68) of infused subjects. The most common serious adverse event (SAE) was Cytokine Release Syndrome (CRS) which was reported in 63.2% (= 43/68) of infused subjects.

10.2 Conclusions and Recommendations

The efficacy results of Study B2202 meet the study objective of demonstrating ORR is greater than the pre-specified null hypothesis rate of 20%. The statistical analysis results support the applicant’s proposed indication for KYMRIAH.