Statistical Analysis Plan I6F-MC-JJCB (a)

A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients

NCT02518113

Approved Date: 17-Jun-2015

# 1. Statistical Analysis Plan
# I6F-MC-JJCB A Phase 1b/Randomized Phase 2 Study to Evaluate LY3039478 in Combination with Dexamethasone in T-ALL/T-LBL Patients



LY3039478, T-ALL/T-LBL

A randomized Phase 1b/2 study to evaluate LY3039478 in combination with dexamethasone in patients with T-ALL/T-LBL.


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Protocol I6F-MC-JJCB
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

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# 3. Revision History

SAP Version 1 was approved prior to the first visit when a subject receives study drug.

# 4. Study Objectives

## 4.1. Primary Objective

The primary objective are as follows:

- Phase 1: to determine the recommended dose of LY3039478 in combination with dexamethasone in
  - adults patients with relapsed/refractory T-ALL/T-LBL (Part A)
  - pediatric patients (Part B)
- Phase 2: to determine if the overall remission rate (ORR) (CR plus CR with incomplete blood count recovery [CRi]) in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone

## 4.2. Secondary Objectives

The secondary objectives of the study are as follows:

- Phase 1:
  - to characterize the safety and toxicity profile of LY3039478 in combination with dexamethasone as assessed by National Cancer Institute (NCI) CTCAE v 4.0
  - to assess the PK parameters of LY3039478 in combination with dexamethasone therapy
  - to document efficacy based on Cheson criteria for leukemia and malignant lymphoma
  - to evaluate gene mutation (eg, NOTCH1/FBXW7/RAS/PTEN) status with efficacy
- Phase 2:
  - to compare the ORR plus partial remission (PR) and PR alone for both arms
  - to assess the remission rate for patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone
  - to assess duration of remission (DoR) = (CR, CRi, and PR)
  - to assess relapse-free survival (RFS), event-free survival (EFS), and OS
  - to compare the safety and toxicity profile of LY3039478 in combination with dexamethasone to dexamethasone and placebo as assessed by NCI CTCAE v 4.0
  - to assess the PK parameters of LY3039478 and dexamethasone in combination therapy
  - to assess patient quality of life using the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)
  - to evaluate gene mutation (eg, NOTCH-1/FBXW7/RAS/PTEN) status with efficacy

## 4.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- to assess clinical utility of the NICD immunohistochemistry (IHC) assay as a potential companion diagnostic for LY3039478
- to evaluate biomarkers in tumor tissue, blood, plasma and cerebrospinal fluid (CSF), which may include, but not be limited to, NICD enzyme-linked immunosorbent assay (ELISA) (or an alternative validated method), gene expression, relevant to the study disease or safety, efficacy, and mechanism of action of LY3039478 and dexamethasone
- to explore PD effects of LY3039478 on biomarkers indicative of Notch activity
- to evaluate the CSF PK of LY3039478

# 5. Study Design

## 5.1. Summary of Study Design

Study JJCB is a multicenter study consisting of a nonrandomized, open-label, dose-escalation Phase 1 study followed by a randomized, double-blind, Phase 2 study in patients with relapsed or refractory T-ALL/T-LBL. The Phase 1 portion of the study will consist of 2 different patient populations, an adult (Part A) and a pediatric (Part B), and will define the recommended dose of LY3039478 in combination with dexamethasone in each of these populations. The randomized Phase 2 study will be a double-blinded, multicenter evaluation to determine if the CR and CRi (CR with incomplete blood count recovery) rate in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone. Figure JJCB.5.1 illustrates the study design.

Eligible adult patients will receive LY3039478 administered orally TIW(3 times per week) and dexamethasone administered 24 mg orally Days 1 to 5 every other week. In Part B (pediatric patients), dexamethasone is administered at 10 mg/m$^2$ BID, orally, Days 1 through 5 every other week. A cycle is defined as 28 days of treatment (4 weeks).

The Phase 1 portion will start with the adult cohort (Part A). The decision to proceed with the pediatric dose exploration (Part B) will be made after safety analysis of the adult cohort.

The dose escalation will be guided primarily by safety assessments from Days 1 through 28 of Cycle 1 for patients in all cohorts. Dose escalation will occur until the MTD is determined. Patients will be enrolled in Part A with the first dose level of 50 mg LY3039478, TIW. Dose levels will be determined based on the review of the safety, PK, and PD data from the previous doses. Additional dose levels (to a maximum of 200 mg TIW) may be explored if necessary. No dose escalation will occur beyond MTD. In Parts A and B, the sample size is estimated to be approximately 13 to 16 patients in each part depending on the relationship between exposure and toxicity as well as the relationship between exposure and pharmacological effects.

After the last patient on Part A has completed Cycle 1 and the recommended dose for the Phase 2 portion is determined, the randomized, Phase 2 portion will begin following an interim review of the data. The patient population in the Phase 2 portion of the study will be identical to the patient population assessed in Part A.

In the Phase 2 portion, 60 patients will be randomized in a 2:1 ratio to receive either LY3039478 in combination with dexamethasone administered 24 mg orally on Days 1 to 5 every other week or placebo in combination with dexamethasone administered 24 mg orally on Days 1 to 5 every other week. Placebo or LY3039478 will be administered orally TIW at the recommended dose from Part A. Patients will receive treatment until progression or meeting discontinuation criteria as outlined in the protocol.

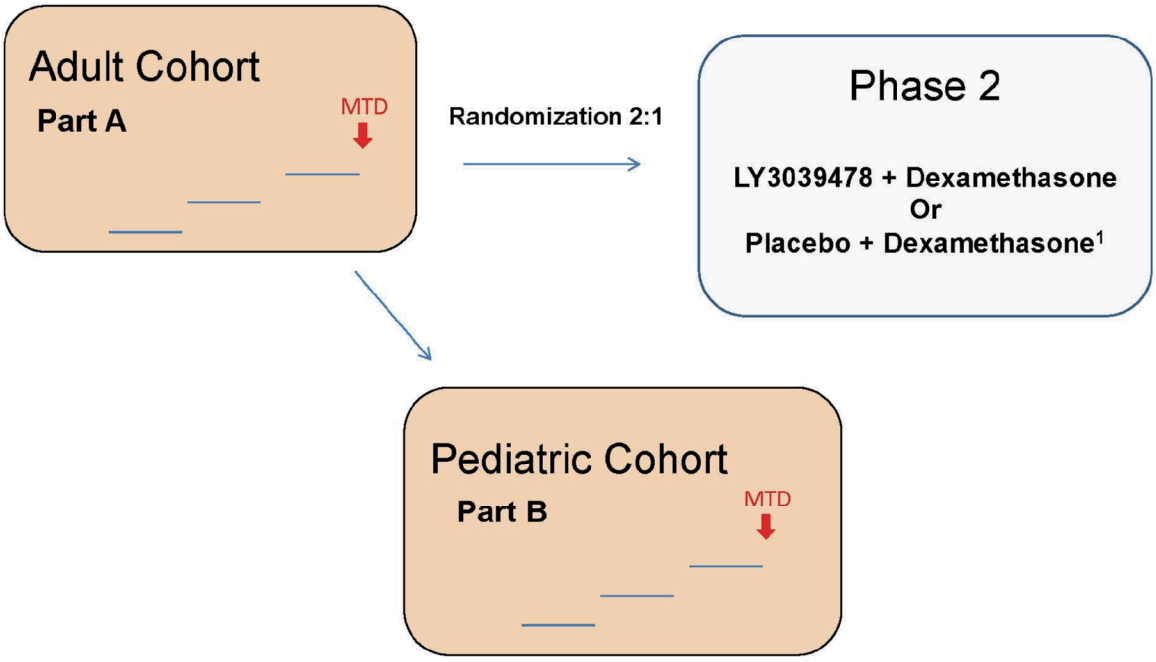
Patients discontinuing the study for treatment failure will be unblinded after discontinuation. A crossover to LY3039478 in combination with dexamethasone will be allowed for patients who were receiving placebo in combination with dexamethasone.

A futility interim analysis will be performed in the Phase 2 portion of the study when 30 patients have completed the CR status determination. The analysis will assess the safety profile, verify that the chosen regimen is clinically feasible, and determine if the futility criteria have been met.

An internal assessment committee consisting of (at minimum) a Lilly Medical Director, a Lilly CRP not associated with the study, a PK scientist, and a statistician will examine the interim results and make recommendations about the trial.

The total sample size for this study is estimated to be approximately 86 to 92 patients.

There is no fixed duration of treatment; patients will remain on study until they fulfill 1 of the criteria for study discontinuation.




[1] Phase 2 patients who discontinue the study due to relapse/refractory disease or treatment failure may crossover to treatment with LY3039478 + Dexamethasone.

Abbreviation: MTD = maximum tolerated dose.

**Figure JJCB.5.1. Illustration of study design.**

## 5.2. Determination of Sample Size

Approximately 86 to 92 patients will be enrolled in this multicenter study.

In the Phase 1 portion of the study, the primary objective is to determine the MTD and the recommended dose for Phase 2. Approximately 13 to 16 patients will be enrolled into the adult (Part A), and approximately 13 to 16 patients will be enrolled in the pediatric (Part B) cohorts sequentially and without randomization to dose. The total sample size per cohort will be determined by DLTs.

In the Phase 2 portion of the study, the primary objective of this study is to compare the ORR (CR plus CRi) rate between LY3039478 administered with dexamethasone and placebo administered with dexamethasone, in adult patients with relapsed/refractory T-ALL/T-LBL. Approximately 60 evaluable patients will be randomized to the 2 treatment arms in a 2:1 ratio (40 randomized to LY3039478 and dexamethasone and 20 randomized to placebo and dexamethasone).

Assuming the ORR for the LY3039478 and dexamethasone arm is 40% and the ORR of the placebo and dexamethasone is 5%, the sample size of 60 evaluable patients will give approximately 82% statistical power to detect the difference, using a 2-sided Fisher's test at the significance level of 0.05, with 1 futility interim once the 30th enrolled patient completes the remission status determination.

Patients who are randomized and do not achieve a CR or CRi will be considered as nonresponders in the primary analysis for ORR.

## 5.3. Method of Assignment to Treatment

### *5.3.1. Phase 1*

Patients who enter the study during the Phase 1 portion will be assigned to receive LY3039478 and dexamethasone. Prior to enrollment into the study, an eligibility check must be conducted (for every patient) between the investigational site and the Lilly clinical research personnel, to confirm that the patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose, cohort, and identification number assignment for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP/CRS.

### *5.3.2. Phase 2*

Patients who enter the study during the Phase 2 portion will be randomized to receive either LY3039478 in combination with dexamethasone or placebo in combination with dexamethasone. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

A dynamic allocation method, introduced by Pocock and Simon (1975) and extended for unequal treatment group sizes by Han et al. (2009), will be adopted to balance patient assignment between treatment arms, using a probability factor of 0.9, based on the following factors:

- age ≤30 years versus >30 years
- T-ALL phenotype versus T-LBL, considered as 6 factors, representing the following 5 phenotypes of T-ALL:

TdT+, variable for all of the following: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD34

  - Pro-T-ALL: cCD3+, CD7+, CD1a-, CD2-, CD4-, CD8-, CD34+/-
  - Pre-T-ALL: cCD3+, CD7+, CD1a-, CD2+, CD4-, CD8-, CD34+/-
  - Cortical T-ALL: cCD3+, CD7+, CD1a+, CD2+, CD4+, CD8+, CD34-
  - Medullary T-ALL: cCD3+, sCD3+, CD7+, CD1a-, CD2+, CD4+or CD8+, CD34-
  - ETP T-ALL: Lack of CD1a and CD8 expression, weak CD5 expression with less than 75% positive blasts, and expression of 1 or more of the following myeloid or stem cell markers on at least 25% of lymphoblasts: CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65

- response to last therapy: refractory/relapse within 1 year of last therapy vs. >1 year

The randomization parameter P will be set to 0.9 to maximize the benefit of the allocation procedure, whilst keeping treatment assignments unpredictable.

# 6. A Priori Statistical Methods

## 6.1. General Considerations

Phase 1 Part A, Phase 1 Part B and Phase 2 study parts will be reported in separate TFLs.

Results of descriptive analyses and estimates from inferential analyses will be presented by dose level cohort (phase 1) or by treatment (phase 2). In the phase 2 study part, an additional group will be included in primary efficacy and safety TFLs to represent data for patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all CIs will be given at a 2-sided 95% level, unless otherwise stated.

The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Any missing longitudinal data will not be imputed, rather estimated from an appropriate random mixed effects model. Transformations will be applied where assumptions behind any analysis are better satisfied by data being transformed onto an alternative scale. All results from any of these analyses will be back transformed to the original scale. Alternatively, nonparametric methods will be applied.

**Table JJCB.6.1. Data Definitions and Rules**

| Term | Definitions or Rule |
|---|---|
| Entered | Patients who have signed the informed consent document directly. |
| Screen failures | Patients who have signed informed consent, do not meet eligibility criteria and are not randomized. |
| Randomized/ Enrolled | Patients who have been assigned to study treatment and but may have not received any study treatment (LY3039478, LY3039478-matched placebo, or Dexamethasone). |
| Patients on therapy | Patients who have been randomized/enrolled to study treatment and have received at least 1 dose of study treatment (LY3039478, LY3039478-matched placebo, or Dexamethasone). |
| Study day | If assessment is on or after date of first LY3039478/ LY3039478-matched placebo dose then<br>(date of assessment) – (date of first study treatment dose) + 1<br>If assessment precedes first treatment dose then<br>(date of assessment) – (date of first study treatment dose)<br>There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose. |
| Cycle day | If assessment is on or after date of first LY3039478/ LY3039478-matched placebo dose then<br>(date of assessment) – (date of first study treatment dose in cycle) + 1<br>If assessment precedes first treatment dose then<br>(date of assessment) – (date of first study treatment dose in cycle)<br>There is no cycle day 0. Cycle day 1 is the date of first dose in the cycle and cycle day -1 is the day before the first dose. |
| Baseline | For change from baseline analysis, baseline value is defined as the last reported measure on or before the first dose date (or discontinuation, if no treatment is given). |
| Study treatment period | Time from treatment start to when the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment. |
| Post-discontinuation – short-term follow-up | The short term follow-up period begins 1 day after discontinuation of study treatment and lasts approximately 30 days (Visit 801). |
| Post-discontinuation – long-term follow-up | The long-term follow-up period begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until patient's death or overall study completion |
| Continued access follow up | The continued access follow up period begins 1 day after the patient and investigator determine that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. |

## 6.2. Adjustments for Covariates

Additional analyses may be performed on efficacy measures to adjust for factors that may affect survival or disease progression.

All of the patient characteristics listed in Section 6.8 will be considered.

## 6.3. Handling of Dropouts or Missing Data

Patients who are randomized and do not achieve a CR or CRi will be considered as nonresponders in the primary analysis for ORR.

The primary method for handling missing time-to-event data will be censoring.

Partial dates will be imputed, with missing day imputed as 15, and missing month and day imputed as 1-July.

## 6.4. Multicenter Studies

This is a multicenter study. Data collected will be analysed as a whole. Exploratory analyses by individual study sites or country may be conducted as warranted.

## 6.5. Multiple Comparisons/Multiplicity

No adjustment for multiplicity is planned for this study. The primary analysis in phase 2 will compare the ORR for LY3039478 plus dexamethasone and placebo plus dexamethasone.

It is not planned to stop the trial early for efficacy, thus there are no adjustments for multiplicity

## 6.6. Analysis Set Definitions

Efficacy analyses will be based on the **intention-to-treat (ITT)** analysis set. This population is defined as all patients randomized to study treatment.

Patients will be grouped according to dose level cohort (phase 1) or randomized treatment (phase 2). Sensitivity analyses may be conducted (if applicable) excluding patients that are randomized but do not receive treatment, and by actual treatment received.

A secondary analysis of the primary efficacy endpoint in phase 2 based upon the **per-protocol set (PPS)** of patients may be performed if there are significant numbers of patients with major protocol deviations (≥10% of total patient population). The PPS is defined as those patients in the ITT set who are compliant with the study protocol. The following criteria will be used in the determination of the PPS

- Inclusion/Exclusion criteria not met which may impact efficacy conclusions: Protocol inclusion criteria [1], [2], [3], [4], [5] and protocol exclusion criteria [13], [19], [20], [21].
- Study drug non-compliance as defined in Section 6.10.
- Received incorrect treatment that affects efficacy analysis
- Received prohibited medications whilst on study treatment, including other chemotherapy, other anticancer therapy, immunotherapy, hormonal cancer therapy

(except therapy of hormone-sensitive prostate cancer patients who are stable on GnRH agonist therapy and breast cancer patients who are stable on antiestrogen therapy (eg, an aromatase inhibitor), radiation, surgery for cancer, or experimental medications.

Safety analyses will be based on the **safety analysis set**, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to actual treatment received.

PD and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

## 6.7. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation).

All entered patients will be accounted for in this summary of disposition. Screen failures and patients who died or discontinued before treatment begins will be specified.

A listing of primary reasons for both study treatment and study discontinuation will also be provided according to each randomized treatment arm.

A summary of all important protocol deviations will be provided.

A listing of patients who discontinued due to AE or death from treatment and study itself will also be provided with additional information on cause of death and the AE associated with discontinuation.

## 6.8. Patient Characteristics

Patient demographics including age, sex, screening height, weight and body mass index, race, ethnicity, patient habits (caffeine/alcohol use) and country will be reported using descriptive statistics.

Baseline disease characteristics will be summarized by cohort (phase 1a, phase 1b) or randomized treatment arm (phase 2). Continuous variables will be summarized by median and range, and compared amongst treatment arms by ANOVA. Categorical variables will be summarized by frequency counts and compared amongst treatment arms by Fishers exact test. Statistical comparisons will be provided in phase 2 where data warrant only. The following disease characteristics will be summarized:

- Sex
- Age
- Diagnosis: T-ALL and T-LBL, with T-ALL additionally split by subtype:

TdT+, variable for all of the following: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD34

  - Pro-T-ALL: cCD3+, CD7+, CD1a-, CD2-, CD4-, CD8-, CD34+/-
  - Pre-T-ALL: cCD3+, CD7+, CD1a-, CD2+, CD4-, CD8-, CD34+/-
  - Cortical T-ALL: cCD3+, CD7+, CD1a+, CD2+, CD4+, CD8+, CD34-
  - Medullary T-ALL: cCD3+, sCD3+, CD7+, CD1a-, CD2+, CD4+or CD8+, CD34-
  - ETP T-ALL: Lack of CD1a and CD8 expression, weak CD5 expression with less than 75% positive blasts, and expression of 1 or more of the following myeloid or stem cell markers on at least 25% of lymphoblasts: CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65
- ECOG status at randomization, or Lanksky status for Phase 1 Part B (pediatrics)
- Disease status: Refractory or relapsed, with relapse additionally split by: first relapse, second relapse, relapse after SCT
- Notch and/or FBWX7 mutational status: Yes, no [See Trinquand et al, 2013 for further details]
- RAS and/or PTEN abnormalities: Yes, no [See Trinquand et al, 2013 for further details]
- Extramedullary disease: Yes, no
- History of CNS leukemia: Yes, no
- Time since initial diagnosis
- Duration of first remission
- Response to last therapy: refractory, or relapsed with duration of remission <1 year, 1-2 years, 2-5 years, >5 years
- Number of prior courses of induction therapy (1, 2, 3, ≥4)
- Country

Other patient characteristics will be summarized as deemed appropriate.

Prior therapies and procedures e.g. stem cell transplant will be listed.

## 6.9. Treatment Compliance

Treatment compliance information for study drug will be collected through pill counts at each visit and the number of tablets taken relative to the number expected to be taken will be summarized.

The patient must take ≥75% of the intended doses to be deemed compliant with study drug administration. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

Percent compliance is calculated from dispensed and returned capsules as:

100 x (total amount of drug taken (mg) / total amount of drug prescribed (mg))

Total amount of drug prescribed is the sum of products of dosing intervals and the expected dose for each interval. Total dose prescribed should take into consideration any dose adjustment(s) before treatment discontinuation date. Treatment compliance will be summarized for LY3039478 and Dexamethosone separately by randomized treatment, cycle, and overall.

## 6.10. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications listings will include both the term reported in CRF and the WHO dictionary term and if concomitant medication use is due to adverse event (AE), the associated AE will also be listed. A separate listing of transfusions will be created.

Anti-cancer systemic therapy, radiotherapy and surgery that occurs post discontinuation of study treatment is captured separately from concomitant medication as the existence of such therapies can lead to censoring of time to event endpoints. Patients that received post discontinuation therapies will be listed by treatment arms.

## 6.11. Efficacy Analyses

Efficacy analyses will be conducted on the ITT analysis set, with patients grouped according to randomized treatment.

The following are definitions of the primary and secondary efficacy endpoints:

**Primary Endpoint:**

**Overall Response Rate (ORR)** is defined as the proportion of patients who achieved a best overall response of either complete remission (CR) or incomplete remission (CRi). The ORR (CR and CRi) is the sum of patients achieving a CR or a CRi divided by the total number of patients randomized in that arm.

**Secondary Endpoints:**

- **Partial Response (PR)** is defined as the proportion of patients who achieved a best overall response of partial remission (PR), out of the total number of patients randomized in that arm.
- **Complete Remission (CR)** is defined as the proportion of patients who achieved a best overall response of complete remission (CR), out of the total number of patients randomized in that arm.
- **ORR and PR** is defined as the proportion of patients who achieved a best overall response of either complete remission (CR), incomplete remission (CRi) or partial remission (PR), out of the total number of patients randomized in that arm.

All of the above endpoints (ORR, PR, CR, ORR and PR) will also be calculated for those patients that cross-over in the Phase 2 part of the trial and receive LY3039478 plus dexamethasone after failure of placebo plus dexamethasone.

- **Overall Survival (OS)** is defined for all patients in the trial, and measured from the date of study enrollment to the date of death from any cause. OS duration is measured from the date of randomization to the date of death from any cause in the Phase 2 portion of the study. For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the

data inclusion cutoff date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

- **Relapse Free Survival (RFS)** is defined only for patients who achieve CR/CRi.

  For T-ALL, RFS is measured from the date of attaining the leukemia-free state until the date of T-ALL relapse or death from any cause, whichever occurs first. Relapsed disease for T-ALL is defined as the reappearance of the blast in the blood or bone marrow (>5%) or any extramedullary site after achievement of a CR.

  For T-LBL, RFS is measured from the time of occurrence of a disease-free state or attainment of a CR to disease recurrence or death as a result of lymphoma or acute toxicity of treatment.

  For a patient who is not known to have relapsed or died by the end of study follow-up, observation of RFS is censored at the date of last contact prior to the data inclusion cutoff, at which an adequate assessment was completed, i.e. blood or bone marrow samples, CT-MRI or PET assessment.

- **Event Free Survival (EFS)** is defined for all patients and measured from the date of entry on study. It is measured until treatment failure, relapse from CR, or death from any cause, whichever occurs first.

  For T-ALL, treatment failure is defined by progressive disease, which is an increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease. For T-ALL patients with preexisting mediastinal disease, progressive disease is defined by a greater than 25% increase in the sum of the product of the greatest perpendicular diameters (SDP) of the mediastinal enlargement.

  For T-LBL, treatment failure is defined as relapsed or progressive disease in protocol Table JJCB.10.1.

  For a patient with none of these events before the end of study follow-up, observation of EFS is censored at the date of last contact prior to the data inclusion cutoff date, at which an adequate assessment was completed i.e. blood or bone marrow samples, CT-MRI or PET assessment. If the patient does not achieve a CR, EFS is defined as the point of treatment failure or death, whichever comes first.

**Censoring Rules for EFS and RFS**

If there are multiple dates associated with one assessment, in order to determine date of progressive or relapsed disease, the assessment date will be set to the first date when the overall response is PD or relapsed disease and the last date otherwise. An EFS or RFS determination is considered adequate if the response is CR, CRi, SD, PD, Relapsed Disease or Refractory.

Table JJCB.6.2 lists censoring rules which will be applied in sensitivity analysis (SA) definitions.

**Table JJCB.6.2. Censoring Rules Sensitivity Analysis Definitions**

| Sensitivity Analysis Definition # | Situation | Date of Progression or Censor | Censored / Progressed |
|---|---|---|---|
| **SA 1** | Patient receives stem cell transplant before relapse, progression or death | Date of stem cell transplant | Censored |
| **SA 2** | Relapsed disease, progressive disease or death after ≥ 2 missed assessments, including blood/bone marrow samples, CT/MRI or PET assessments. | Date of last post baseline assessment before missed assessments or Date of randomization (for EFS) or disease-free state (for RFS) if no other assessment in between | Censored |
| **SA 3** | Patient dose not have adequate baseline assessment (bone marrow biopsy/aspirate or PET-CT, or CT-MRI) | Date of randomization for EFS analysis Patient not eligible for RFS analysis | Censored |
| **SA 4** | Patient is lost to follow-up without relapsed or progressive disease | Date of next scheduled post baseline adequate assessment at or after becoming lost to follow-up | Progressed |
| **SA 5** | Patient is lost to follow-up without relapsed or progressive disease | Date of next scheduled post baseline adequate assessment at or after becoming lost to follow-up | Progressed for the treatment arm and censored for the control arm |

- **Duration of Response (DoR)** DoR for T-ALL is measured from the date of CR, CRi or PR by blood count recovery and bone marrow examination, until the date of relapse. DoR for T-LBL is measured from the time when criteria for response (ie, CR or PR) are met, until the first documentation of relapse or progression. For patients who die without report of relapse, DoR is censored on the date of death, regardless of cause. For a patient with no report of relapse or death by the end of the follow-up data collection, observation is censored at the date of last contact prior to the data inclusion cutoff date.

### 6.11.1. Primary Outcome and Methodology

In the Phase 1 portion, the primary outcome of interest is determining the MTD and recommended dose for Phase 2. Efficacy data will be tabulated and listed, no formal hypothesis testing is planned.

In the Phase 2 portion, the primary efficacy endpoint of ORR (CR plus CRi) rate and its exact 95% confidence interval (CI) will be estimated for each treatment arm. The proportion in each treatment arm will be compared using Fisher's exact test. Primary analysis will utilize the ITT analysis set.

Best response will be derived to encompass all tumor assessments from baseline until the earliest objective progression or start of new anticancer therapy. Primary analysis for ORR will be conducted once all enrolled patients have completed 3 cycles of treatment, discontinued treatment, started new anticancer therapy or met criteria for objective progression. Patients who are randomized and do not achieve a CR or CRi will be considered as nonresponders in the primary analysis for ORR.

### 6.11.2. Additional Analyses of the Primary Outcome

Sensitivity analyses of the primary outcome measure will include a re-randomization test. The observed responses and randomization stratification covariates will be considered as a set of fixed values, and the treatment assignment then re-randomized using the same allocation mechanism from the trial. Approximately 5000 re-randomizations will be performed and the resulting p-values evaluated by:

- Comparing the observed difference in proportion of ORR with the re-randomized treatment differences
- Comparing the observed Fisher's test p-value for the comparison of treatments with the re-randomized treatment comparison.

### 6.11.3. Secondary Efficacy Analyses

**Response Endpoints**

The secondary efficacy endpoints of ORR and PR, PR and CR, and their exact 95% CIs will be estimated for each treatment arm and compared by 2-sided Chi-squared test or Fisher's exact test between 2 arms. A Fisher's exact test will be chosen over a Chi-squared test if in the 2x2 table, any of the expected cell counts are less than 5, or any cell has zero counts.

Efficacy data (CR, CRi, PR, and ORR) for patients receiving LY3039478 in combination with dexamethasone after failure of placebo in combination with dexamethasone will be tabulated, and further exploratory analyses of efficacy data conducted as warranted.

**Time to Event Endpoints**

For the secondary efficacy endpoints OS, RFS, and EFS, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves as well as survival rates at various

prespecified time points (12 months for OS, 6 and 12 months for RFS and EFS) for each treatment arm.

The secondary efficacy endpoint DoR is subject to competing risk of death without relapse; therefore, the cumulative incidence of relapse (Gray 1988; Pepe and Mori 1993; Gooley et al. 2001) will be used. In the calculation, patients who did not have the event will be considered right-censored observations.

The comparison of the survival curves between treatment groups will be conducted by a log-rank test. Exploratory analyses for the comparison of the survival curves between treatment groups may additionally be conducted by a stratified log-rank test with some of the following stratification variables: initial diagnosis (T-ALL phenotype, T-LBL), response to last therapy (refractory or relapsed), age, number of prior therapies (≤2, >2), NOTCH-1/FBXW7/RAS/PTEN status.

The Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the hazard ratio and corresponding 95% CI with Wald's test p-value after adjusting for the following potential predictive/prognostic variables: initial diagnosis (T-ALL phenotype, T-LBL), response to last therapy (refractory or relapsed), age, number of prior therapies (≤2, >2), NOTCH-1/FBXW7/RAS/PTEN status.

The unadjusted impact of patient baseline disease characteristics listed in Section 6.8 on OS and EFS will be explored using Cox proportional hazard models (Cox 1972) with the baseline characteristic as a factor (continuous variables split at median) and the hazard ratio and corresponding 95% CI plotted on a forest plot. Any characteristics found to be significant prognostic markers for EFS or OR may be included as additional covariates in COX proportional hazard model analyses to compare treatment arms.

### *6.11.4. Sensitivity Analyses*

For the analysis of time-to-event endpoints EFS and RFS, sensitivity analysis definitions as described in table JJCB.6.2 will be completed for the log-rank test. Such analyses will only be conducted if the primary analysis of such endpoints warrants sensitivity analysis to evaluate whether and to what extent the conclusion would be affected under the different censoring rules.

For the analysis of OS, sensitivity analysis definition SA1 as described in Table JJCB.6.2 will also be completed. Further analyses may explore OS adjusting for patients which received LY3039478 plus dexamethasone following treatment failure of placebo plus dexamethasone, if warranted.

Additionally, analyses may be conducted (if applicable) excluding patients that are randomized but do not receive treatment, and by actual treatment received.

## 6.12. Health Outcomes/Quality-of-Life Analyses

### *6.12.1. Patient-Reported Outcomes*

The FACT-Leu includes the 27-item cancer-specific Functional Assessment of Cancer Therapy-Leukemia-General (FACT-G) that assesses physical, social/family, emotional and functional well-being plus a 17-item subscale that assesses additional concerns specific to leukemia. Methods for handling missing data, reverse scoring and other scoring guidelines are provided in Appendix 1.

FACT-Leu results will be summarized descriptively by cycle and for postdiscontinuation visits, including number of completed questionnaires, compliance rates, reasons for noncompliance, scores for each scale, subscale and total scores, and changes from baseline.

Each of the 5 subscales, plus the Leukaemia trial outcome index, FACT-G total score and FACT-Leukaemia total score will be analysed by mixed effect model repeated measures. The model will include randomized treatment, cycle and the interaction of randomized treatment and cycle as fixed effects, with baseline and the interaction of baseline and cycle as a covariate. An unstructured variance covariance matrix will be used, provided data permit. Otherwise the following variance covariance structures will be tested and that with the best fit according to AIC selected: compound symmetry, heterogeneous Toeplitz, first-order autoregressive combined with random patient effect, heterogeneous autoregressive, or heterogeneous compound symmetry. The Kenward-Roger method will be used to estimate denominator degrees of freedom. Least square means and treatment comparisons with corresponding 95% confidence intervals (CIs) for each cycle will be presented in tabular and graphical displays.

### *6.12.2. Resource Utilization*

Investigators will be asked to document the use of best supportive care measures, concomitant medications, transfusions, and disease/adverse event-related hospitalization days. Such assessments are to be taken throughout the Phase 2 portion of the study, through the 30-day short-term follow-up, and during the postdiscontinuation follow-up visit.

The proportion of patients receiving concomitant medications for supportive care, and each type of WHO drug name will be summarized by randomized treatment and cycle, including overall cycles, and compared using fishers exact test. Further exploratory analyses may be conducted if warranted, for example the mean number of doses for medications administered to at least 10% of phase 2 patients.

The proportion of patients receiving transfusions will be summarized by randomized treatment and cycle, including overall cycles, and compared between treatment arms using a fishers exact test. Further analyses adjusting for covariates may be conducted if warranted.

The number of hospitalization days, and number of platelet and RBC transfusions, will be summarized descriptively by randomized treatment and cycle.

## 6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

The Lilly pharmacokineticist will be responsible for PK and PK/PD analysis.

PK analyses will be conducted on patients who receive at least 1 dose of the study drug and have samples collected. PK parameter estimates for plasma and CSF LY3039478 and plasma dexamethasone, where possible, will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be $C_{max}$, area under the plasma concentration-time curve from time zero to last measurable plasma concentration ($AUC_{[0\text{-}tlast]}$), area under the concentration-time curve from time zero to infinity or over 1 dosing interval at steady state ($AUC_{[0\text{-}\infty]}$ or $AUC_{\tau}$). Other noncompartmental parameters, such as $t_{1/2}$, apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetics management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and PD effect (eg, Aβ), data permitting. This model may be used to help reassess the dose cohort escalation as the study progresses. If deemed necessary, PK/PD modeling may be employed to evaluate variability in exposure, pharmacologic effects, and safety parameters.

### *6.13.1. Pharmacodynamics and Tailoring Analyses*

Biomarker data from all patients undergoing biomarker assessments will be analyzed using descriptive statistics. Biomarkers (including NICD and gene expression) will be explored at baseline for prognostic value in ORR, EFS or OS outcome, and for potential predictive value in an efficacious response to treatment.

ORR will be summarized by gene mutation status (eg, NOTCH-1/FBXW7/RAS/PTEN) and presented in tabular and graphical displays. Interaction effect between the gene mutation statuses may be further analyzed as warranted.

Further exploratory analyses of pharmacodynamic markers will be conducted as warranted.

## 6.14. Safety Analyses

All safety summaries and analyses will be based upon the safety population that includes patients that have received at least one dose of study drug. Safety analyses will be conducted according to actual treatment received. Data collected for patients receiving LY3039478 plus Dexamethosone following treatment failure of placebo plus dexamethasone included as an additional treatment group in TFLs.

Safety data will be listed and summarized with patient counts and percentages in each treatment arm. Details of the analyses are described in the following sections.

### *6.14.1. Extent of Exposure*

The number of dose omissions, reductions, delays, and cycles received and the dose intensity will be summarized for all treated patients per treatment arm. Summarized data will be provided for the period prior to first CR, the period following first CR, and the total treatment period.

Percent dose intensity is calculated as:

100 x (actual cumulative dose taken (mg) / planned cumulative dose (mg))

Note that planned dose is the same as actual dose if there is no dose modification or cycle delays. Reasons for dose adjustments will also be summarized, and if the reason for dose modification is due to AE, the associated AE will be provided.

### *6.14.2. Adverse Events*

A listing of all adverse events by patient will be presented. This listing will include patient number, adverse event (actual term and preferred term), event start and end dates, CTCAE grade, relationship to study drug/procedure, seriousness, and outcome. A listing of SAE will be produced using the similar format.

An overall summary will be provided for AEs. The number and percent of evaluable patients will be summarized by treatment for each category below. The summary will provide counts for all AEs, and AEs possibly related to study treatment.

- Patients with at least one TEAE
- Patients with at least one grade 3 or 4 TEAE
- Patients with at least one SAE
- Patients who discontinued due to AE
- Patients who discontinued due to SAE
- Patients who died due to AE on study treatment
- Patients who died due to AE within 30 days of discontinuation from study treatment

**Treatment-emergent adverse events (TEAE)** are defined as follows:

- Any event that first occurred or worsened in severity after baseline, based on the MedDRA LLT term and CTCAE severity grade. This means that any episode of the same AE with the same grade as at baseline that starts after the first dose of study treatment will not be defined as treatment emergent, even if now considered possibly drug related.
- Or any PEC (emerged prior to informed consent) or any AE (emerged after signed informed consent) that were still present prior to first dose but has increased in severity (CTCAE grade) following the start of treatment, regardless of causality.

As per Lilly's standard operating procedures, all "probably related," "possibly related," or "does not know" AEs and SAEs will be defined as related to study drug.

MedDRA v16.1 (or higher) will be used when reporting AEs by MedDRA terms. TEAEs will be summarized by SOC and by decreasing frequency of preferred term (PT) within SOC.

TEAEs will be summarized by CTCAE grade, including the total for maximum Grade 3 and 4, and Grade 3, 4 and 5. These summaries will be provided for events regardless of study drug causality, and repeated for events deemed by the investigator to be possibly related to study medication.

Laboratory parameter abnormalities will be summarized by CTCAE grade.

#### 6.14.2.1. Dose Limiting Toxicity

Dose limiting toxicities (DLT) will be listed for all patients on therapy in Phase 1. DLT-equivalent toxicities will also be listed for all patients on therapy in Phase 1 and Phase 2.

In Phase 1 of the study, dose escalation will be driven by safety using a modified 3+3 scheme, with incorporation of model-based dose escalation (Neuenschwander et al. 2008) to assist in estimation of DLT rate at recommended dose level.

A model-based method that incorporates prior expectations about the dose-toxicity curve and controls for over-dosing probability will be applied to the data at the end of each cohort, which will provide quantitative guidance to the investigators and Lilly CRP to help determine the next dose level. Prior expectations about the dose-toxicity curve will be based on observed DLT rates in Study JJCA. After incorporation of observed DLT rates in this study, the posterior probability of a DLT at each dose level will be categorized to 4 bands:

- under-dosing: the probability of a DLT at a given dose level in (0, 0.20)
- targeted toxicity: the probability of a DLT at a given dose level in (0.20, 0.35)
- excessive toxicity: the probability of a DLT at a given dose level in (0.35, 0.60)
- unacceptable toxicity: the probability of a DLT at a given dose level in (0.60, 1.00)

The model aims to recommend a dose which maximizes the probability of targeted toxicity, while controlling the probability of excessive or unacceptable toxicity to less than 25%. The maximum increment of escalation will be no more than 100%. The exact increment will be determined by the investigators and Lilly CRP and may be less than the model prediction or <100%.

Further details on the derivation of a prior for DLT rate and simulations on the dose escalation model are provided in a separate simulation plan document.

### *6.14.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events*

All deaths in this study, including the reasons for death, will be listed by treatment. The reasons for death will be also summarized separately for on-therapy, within 30 days of last dose of study drug and during the long term follow-up periods.

### *6.14.4. Clinical Laboratory Evaluation*

Listings of all laboratory results will be provided (using SI units [International System of Units], when available) by treatment, for hematology, chemistry, urinalysis, ECG chemistry, immune phenotype, coagulation, CSF and bone marrow. Normal reference ranges, percent of the result outside of range (result divided by lower limit if result is less than lower limit; result divided by higher limit if result is greater than higher limit) and percent change from baseline will also be included. Seected laboratory parameters may be plotted by time.

Laboratory analytes below/above quantifiable levels (data in the database recorded as "<x" and ">x) will be reported as such in listings, and imputed to the lower or upper limit of quantification in any summarise or analyses.

Neutrophils, platelets, lympthocytes, monocytes, eosinophils, basophils, RBC, WBC, Nucleated RBCs (NRBC)/100 WBC blasts and other laboratory parameters of interest to disease status will be plotted by time. Data will be log transformed and the logged ratio to baseline analysed by mixed effect model repeated measures with treatment, cycle, and the interaction of treatment and cycle as fixed effects, with baseline and the interaction of baseline and cycle as a covariate. An unstructured variance covariance matrix will be used, data permitting. Otherwise, the following variance covariance structures will be tested and that with the best fit according to AIC selected: compound symmetry, heterogeneous Toeplitz, first-order autoregressive combined with random patient effect, heterogeneous autoregressive, or heterogeneous compound symmetry. The Kenward-Roger method will be used to estimate denominator degrees of freedom. Geometric means and treatment comparisons with corresponding 95% confidence intervals (CIs) for each cycle will be presented in tabular and graphical displays.

A waterfall plot will be provided for minimum percentage bone marrow blasts by treatment arm, coloured by gene mutation status.

A calculated CTCAE grade using CTCAE v4.0 (or higher) will be provided for all laboratory results which can be used independently of clinical judgment to determine a CTCAE severity grade.

### *6.14.5. Vital Signs and Other Physical Findings*

Vital signs measurements including height, weight, temperature, blood pressure and post-baseline ECOG or Lanksy performance status will be listed by treatment arm.

### *6.14.6. Electrocardiograms*

Electrocardiogram (ECG) assessment of normality and clinical significance will be listed by treatment group. Myocardial information and quantitative results including PR, QRS, QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR intervals will provided in patient listings for absolute and change from baseline. In addition, summaries of outlying corrected QT intervals (QTc, QTcB and QTcF) will be provided by treatment. Outlying intervals include absolute values > 450, >480 and >500 msec and change from baseline >30 and >60 msec.

Further exploratory analyses may be conducted as warranted.

## 6.15. Subgroup Analyses

Exploratory subgroup analyses of efficacy endpoints will be performed for stratification or potential prognostic variables as listed in Section 6.8. Other subgroup analyses may be performed as deemed appropriate.

## 6.16. Protocol Violations

Protocol violations will be identified based on information recorded on the investigator log and through statistical programming of the data. A list of data dependent protocol violations in general and specific to this study is as follows:

**General:**

- Inclusion/Exclusion criteria not met which may impact efficacy conclusions: Protocol inclusion criteria [1], [2], [3], [4], [5] and protocol exclusion criteria [13], [19], [20], [21].
- Study drug non-compliance as defined in Section 6.10.
- Received incorrect treatment that affects efficacy analysis
- Received prohibited medications whilst on study treatment, including other chemotherapy, other anticancer therapy, immunotherapy, hormonal cancer therapy (except therapy of hormone-sensitive prostate cancer patients who are stable on GnRH agonist therapy and breast cancer patients who are stable on antiestrogen therapy (eg, an aromatase inhibitor), radiation, surgery for cancer, or experimental medications.
- Informed consent violations
- If patient with “entry criteria not met” is marked at screening but patient moves on to cycle 1

**Study specific:**

- For Cycle 2 and beyond, a delay of >7 days in the start of a cycle (Dose 1) for any reason other than recovery from toxicity, or a delay of >21 days in the start of a cycle (Dose 1) for any reason.
- Failure to obtain bone marrow biopsy and/or aspirate samples, or tumor biopsy (T-LBL patients) (at screening only)
- Crossover to LY3039478 plus dexamethosone without documented treatment failure on placebo plus dexamethasone.
- Failure to perform safety procedures or missing safety measurements per requirements in Study Schedule (Attachment 1 in Protocol)
    - Hematology/chemistry
    - ECG

  Note: only collections “not done” are considered significant protocol violations.

This list of these protocol violations may be included in a patient listing, and patients with missing safety assessments will identified from a tabular display of individual patient assessment according to study schedule. These data dependent protocol violations, together with the data from the investigator log will be summarized to include only important protocol violations for the final study report.

## 6.17. Interim Analyses and Data Monitoring

**Phase 1:** The Phase 1 portion is a nonrandomized, open-label study, and no interim analyses are planned until the end of Phase 1. Patient safety will be assessed prior to each dose escalation to ensure nothing precludes administration of larger doses to future study patients. In addition to reviewing AEs and laboratory measurements, PK and PD profiles (if available) of LY3039478 will be reviewed per cohort. Based on these interim results, modifications (for example, reductions in dose increment) to the dose-escalation strategy or other design elements may be made to ensure patient safety. The study investigators and the Lilly CRP will make the determination regarding dose escalation based on their review of the safety/tolerability data and the PK/PD data from the previous cohorts. An interim analysis including safety, PK, and PD data will be conducted prior to proceeding to the Phase 2 portion of the study. All relevant data will be reviewed to confirm the estimation of the MTD. The decision to proceed to Phase 2 will be made following discussions between the investigators and Lilly clinical research personnel and documented in writing.

**Phase 2:** An Assessment Committee will be established prior to the inclusion of the first patient in the phase 2 portion of the trial. The AC will review unblinded interim analyses of safety and efficacy data. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

In the Phase 2 portion, safety interim analyses are planned every 12 months, and at the planned futility interim analysis, when response data from 30 randomized patients have been obtained. There are no prespecified rules for stopping the trial due to safety concerns. The assessment committee members will review unblinded safety data at each interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.

One futility interim analysis is planned in Phase 2 once 30 patients are randomized and have completed the CR status determination. PK and/or PD data, if available, will also be reviewed at this interim analysis. Given the small sample size per treatment arm at the interim analysis: n=10 for the placebo plus dexamethasone (control) arm, and n=20 for the LY3039478 plus dexamethasone (test) arm, and the low anticipated ORR for the control arm (<=5%) in this study, no formal inferential analysis is planned at the interim analysis. The AC may recommend to stop the study for futility if the observed improvement in response rates is less than 5%. For example, if the control arm has 1 response in 10 patients (10%), the test arm would need to observe at least 3 responses in 20 patients (15%) to warrant continuing the study. This decision criterion is

provided to the AC for guidance only. Any recommendation to stop for futility will be based on AC review of all available safety and efficacy data in addition to ORR rate.

Simulations have been conducted in order to understand the operating characteristics of the futility rule and the impact on statistical power is considered minimal. It is not planned to stop the trial early for efficacy, thus there are no adjustments for multiplicity.

Only the assessment committee is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

## 6.18. Annual Report Analyses

The following reports are needed for the DSUR:

1. Estimated cumulative subject exposure
2. Cumulative exposure to investigational drug, by demographic characteristics for ongoing unblinded clinical trials and completed clinical trials
3. Exposure information for ongoing clinical trials and clinical trials that completed during the reporting period
4. Listing of subjects who died during the DSUR period
5. Discontinuations due to adverse event during the DSUR Period.

For guidance on creation of these reports, see the DSUR collaboration site (http://lillynetcollaboration.global.lilly.com/sites/GMRS_GPS/Surv/dsur/default.aspx?PageView=Shared)

## 6.19. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) and EudraCT requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.

- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

Analyses provided for the EudraCT requirements include the following:

- Summary of adverse events, provided as a dataset which will be converted to an XML file, in accordance with EudraCT requirements.
- Categorical breakdown of age across the entire study, represented planned and actual number of patients for the following age groups: infants and toddlers (28 days-23 months), children (2-11 years), adolescents (12-17 years), adults (18-64 years, 65-84 years and 85 years and over).

For the purpose of CTR/ EudraCT reporting, patients who have died, or are still in the study but off treatment, at primary DBL will be considered a completer. Those that withdrew consent for all procedures, including follow-up, or were lost to follow up, will be considered as early discontinuers. Patients who remain on treatment will be counted as continuing treatment.

# 7. References

Gooley TA, Leisenring W, Crowley J, Storer BE. Why Kaplan-Meier fails and cumulative index succeeds when estimating failure probabilities in the presence of competing risks. In: Crowley J, Hoering A, Ankerst D, editors. Handbook of Statistics in Clinical Oncology. New York: Marcel Dekker; 2001:p 513-524.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc*. 1958;53(282):457-481.

Trinquand A et al. Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenetic risk classification or adult t-cell acute lymphoblastic leukemia: A group for research in adult acute lymphoblastic leukemia study. *Journal of Clinical Oncology*. 2013; 31:4333-4342.

# 8. Appendices

# Appendix 1. FACT-Leukemia Scoring Guidelines

The following information has been downloaded from http://www.facit.org/FACITOrg/Questionnaires

## FACIT Administration and Scoring Guidelines

### Scoring the FACT-G:

The FACT-G scoring guide identifies those items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score**. For all FACIT scales and symptom indices, the higher the score the better the QOL.**

Handling missing items. If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

**Prorated subscale score =** [Sum of item scores] **x** [N of items in subscale] ÷ [N of items answered]

When there are missing data, prorating by subscale in this way is acceptable as long as **more than** 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The total score is then calculated as the sum of the un-weighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as **overall item response rate** is greater than 80% (e.g., at least 22 of 27 FACT-G items completed). This is not to be confused with individual subscale item response rate, which allows a subscale score to be prorated for missing items if greater than 50% of items are answered. In addition, a total score should only be calculated if ALL of the component subscales have valid scores.

### Scoring the Specific Scales & Symptom Indices:

For the "Additional Concerns" subscale (e.g., cancer-specific questions) and the symptom indices, the procedure for scoring is the same as described above for the FACT-G. Again, **over** 50% of the items (e.g., 5 of 9 items, 7 of 12 items) must be completed in order to consider each subscale score valid.

### Deriving a Total Score:

The total score for the specific FACIT scales is the sum of the FACT-G (the first 4 subscales common to almost all scales) plus the "Additional Concerns" subscale. The symptom indices do not include the FACT-G in the total score. By following this scoring guide and transcribing the FACT-G score, the two totals can be summed to derive the **TOTAL FACT/FACIT SCORE**.

## FACT-Leukemia Scoring Guidelines (Version 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.

4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-Leukemia).

5. **The higher the score, the better the QOL.**

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **PHYSICAL** | GP1 | 4 | - | _____ | =_____ |
| **WELL-BEING** | GP2 | 4 | - | _____ | =_____ |
| **(PWB)** | GP3 | 4 | - | _____ | =_____ |
| | GP4 | 4 | - | _____ | =_____ |
| *Score range:* 0-28 | GP5 | 4 | - | _____ | =_____ |
| | GP6 | 4 | - | _____ | =_____ |
| | GP7 | 4 | - | _____ | =_____ |

***Sum individual item scores:*** _____

***Multiply by 7:*** _____

***Divide by number of items answered:*** _____=**PWB subscale**

| | | | | | |
|---|---|---|---|---|---|
| **SOCIAL/FAMILY** | GS1 | 0 | + | _____ | =_____ |
| **WELL-BEING** | GS2 | 0 | + | _____ | =_____ |
| **(SWB)** | GS3 | 0 | + | _____ | =_____ |
| | GS4 | 0 | + | _____ | =_____ |
| *Score range:* 0-28 | GS5 | 0 | + | _____ | =_____ |
| | GS6 | 0 | + | _____ | =_____ |
| | GS7 | 0 | + | _____ | =_____ |

***Sum individual item scores:*** _____

***Multiply by 7:*** _____

***Divide by number of items answered:*** _____=**SWB subscale**

| | | | | | |
|---|---|---|---|---|---|
| **EMOTIONAL** | GE1 | 4 | - | _____ | =_____ |
| **WELL-BEING** | GE2 | 0 | + | _____ | =_____ |
| **(EWB)** | GE3 | 4 | - | _____ | =_____ |
| | GE4 | 4 | - | _____ | =_____ |
| *Score range:* 0-24 | GE5 | 4 | - | _____ | =_____ |
| | GE6 | 4 | - | _____ | =_____ |

***Sum individual item scores:*** _____

***Multiply by 6:*** _____

***Divide by number of items answered:*** _____=**EWB subscale**

| | | | | | |
|---|---|---|---|---|---|
| **FUNCTIONAL** | GF1 | 0 | + | _____ | =_____ |
| **WELL-BEING** | GF2 | 0 | + | _____ | =_____ |
| **(FWB)** | GF3 | 0 | + | _____ | =_____ |
| | GF4 | 0 | + | _____ | =_____ |
| | GF5 | 0 | + | _____ | =_____ |
| *Score range:* 0-28 | GF6 | 0 | + | _____ | =_____ |
| | GF7 | 0 | + | _____ | =_____ |

***Sum individual item scores:*** _____

***Multiply by 7:*** _____

***Divide by number of items answered:*** _____=**FWB subscale**

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **LEUKEMIA** | BRM3 | 4 | - | _____ | =_____ |
| **SUBSCALE** | P2 | 4 | - | _____ | =_____ |
| **(LEUS)** | BRM2 | 4 | - | _____ | =_____ |
| | ES3 | 4 | - | _____ | =_____ |
| *Score range:* 0-68 | LEU1 | 4 | - | _____ | =_____ |
| | TH1 | 4 | - | _____ | =_____ |
| | TH2 | 4 | - | _____ | =_____ |
| | HI12 | 4 | - | _____ | =_____ |
| | BMT6 | 4 | - | _____ | =_____ |
| | C2 | 4 | - | _____ | =_____ |
| | C6 | 0 | + | _____ | =_____ |
| | An7 | 0 | + | _____ | =_____ |
| | N3 | 4 | - | _____ | =_____ |
| | LEU5 | 4 | - | _____ | =_____ |
| | LEU6 | 4 | - | _____ | =_____ |
| | BRM9 | 4 | - | _____ | =_____ |
| | LEU7 | 4 | - | _____ | =_____ |

***Sum individual item scores:***_____

***Multiply by 17:*** _____

***Divide by number of items answered:*** _____**=LEU Subscale**

**To derive a FACT-Leukemia Trial Outcome Index (TOI):**
*Score range:* 0-124

_____ + _____ + _____ =_____**=FACT-Leukemia TOI**

(**PWB** score) (**FWB** score) (**LeuS** score)

**To Derive a FACT-G total score:**
*Score range:* 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

**To Derive a FACT-Leukemia total score:**
*Score range:* 0-176

_____ + _____ + _____ + _____ + _____ =_____=**FACT-Leukemia Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**LeuS** score)