NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Korean Post Marketing Surveillance study to observe safety and effectiveness of BESPONSA®
Protocol number	B1931027
Protocol version identifier	Amendment 4
Date of last version of protocol	07 Nov 2023
Active substance	Inotuzumab ozogamycin (**L01XC26**)
Medicinal product	BESPONSA® Injection
Research question and objectives	The objective of this study is to monitor usage of BESPONSA® in real practice including adverse events on BESPONSA®.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
CCI	
AE	Adverse Event
AEM	Adverse Event Monitoring
ALL	Acute Lymphoblastic Leukemia
ANC	Absolute Neutrophil Count
ADL	Activities of Daily Living
BSA	Body Surface Area
CI	Confidence Interval
CR	Complete response /Complete remission
CRF	Case Report Form
CRi	Complete response with incomplete blood count recovery /Complete remission with incomplete hematologic recovery
CTCAE	Common Terminology Criteria for Adverse Events
HCT	Hematopoietic Cell Transplant
IEC	Independent Ethics Committee
IgG4	Immunoglobulin type G, subtype 4
IRB	Institutional Review Board
MFDS	Ministry of Food and Drug Safety
NCI	National Cancer Institute
NI	Non-Interventional
NIS	Non-Interventional Study
PMS	Post-Marketing Surveillance

RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRSD	Single Reference Safety Document
VOD/SOS	Veno-Occlusive liver Disease/ Sinusoidal Obstruction Syndrome

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Ju-Won Woo, B.Pharm, MBA	Non-Interventional Study Lead	Pfizer Pharmaceuticals Korea Ltd	Seoul, Korea

3. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1	13Nov 2018	2.Responsible parties	Change of Principal Investigator(s) of the Protocol	Resignation of responsible colleague
		7.3.8.3. Adverse events data collection	Change of category for action/outcome	Align with *AEM01 - Form guidance - NIS WITH Stipulated Collection of AEs/Pragmatic Non-Medicinal Interv Study Completion Guide (V6:Aug-2016)*
		7.4. Sample size	Description the Section of Regulation on Approval and Review of Biological Products and re-state the reference for sample size	Describe relevant law in detail and state more proper reference for sample size
		7.5.Data source 7.5.2 Record retention 7.6.1 CRFs/DCTs /Electronic data record 8. Protection of human subjects	Delete duplicated section and move some section to 7.6.1 Move to 7. 6. 2 Add data management section Re-state in detail	Align with *CT24-WI-GL02-RF01 1.0* Non-Interventional Study Protocol Template For Primary Data Collection Study *15-Aug-2018*
Amendment 2	27Mar2019	4. Milestones	Change of Planned date for milestones	Change of Planned date according to the actual date of BESPONSA® approval.
		7.2.3. Duration of the study	Add definition in the duration of the study	Due to MFDS corrective order
Amendment 3	19 Jun 2023	2.Responsible parties	Change of Principal Investigator(s) of the Protocol	Resignation of responsible colleague
		5. Rationale and background	Change of the number of subjects Update result of Phase 3 INO-VATE study	Changes based on the adjustment application for the number of subjects To reflect final result
		7.2.3. Duration of the study	Change of the number of subjects	Changes based on the adjustment application for the number of subjects
		7.4. Study Size	Change of the number of subjects	Changes based on the adjustment application for the number of subjects
Amendment 4	07 Nov 2023	5. Rationale and background	Change of the number of subjects	Changes based on the adjustment application for the number of subjects
		7.2.3. Duration of the study	Change of the number of subjects	Changes based on the adjustment application for the number of subjects
		7.3.8.2. Definition of serious adverse events (SAEs)	Revision of description for Hospitalization	Reflection of the updated Pfizer SOP template
		7.4. Study Size	Change of the number of subjects	Changes based on the adjustment application for the number of subjects
		7.6.2. Record	Changes of record retention	Reflection of the updated Pfizer SOP

		retention	period	template
		9.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours	Revision of description for Exposure during pregnancy	Reflection of the updated Pfizer SOP template

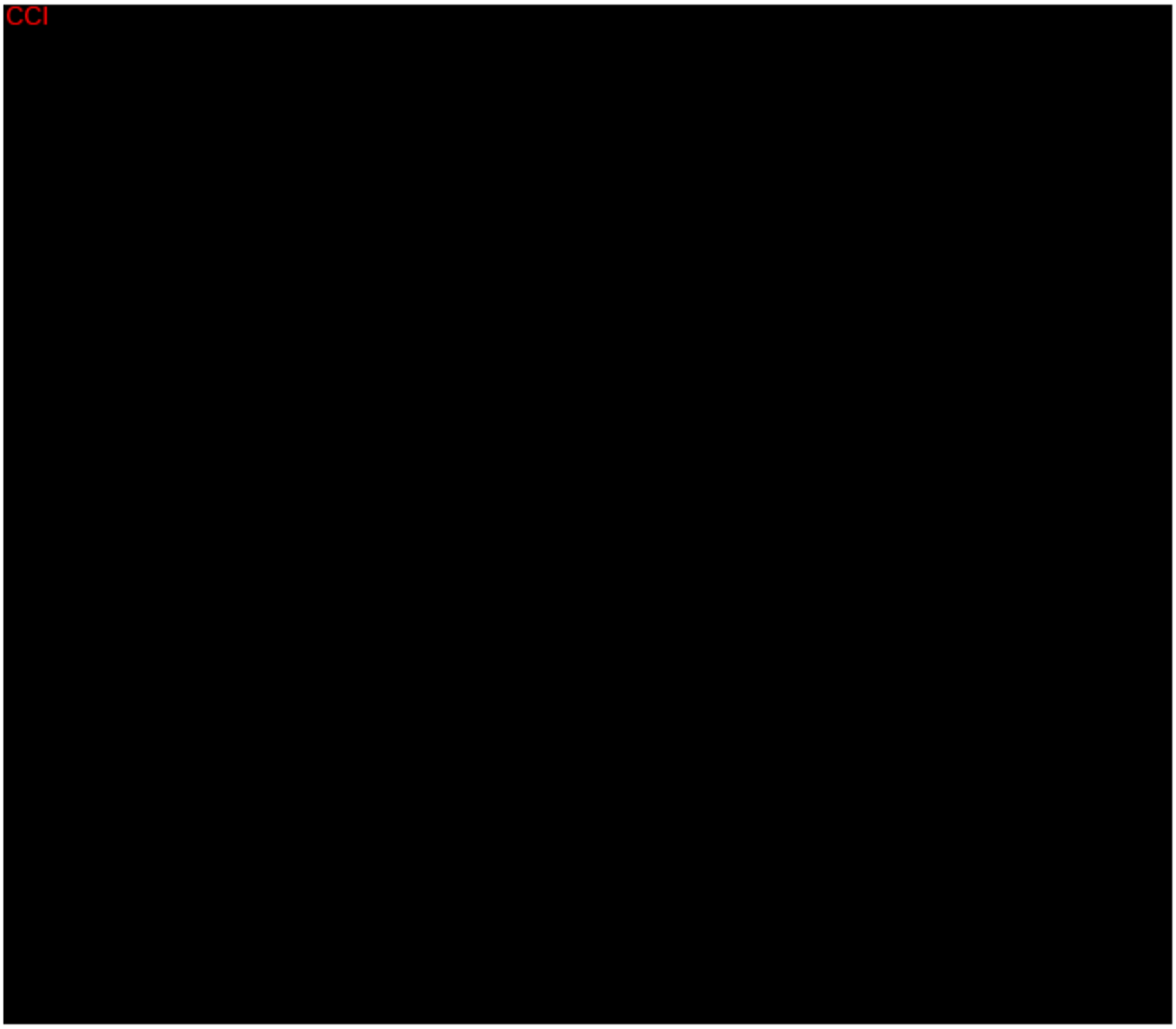
4. MILESTONES

Milestone	Planned date
BESPONSA® approval	3 Jan 2019
Start of data collection	1 Jun 2019
End of data collection	2 Jan 2025
Interim report As required by MFDS regulations, the periodic interim report along with RMP report would be submitted to MFDS every 6 months for the first two years and then annual report would be submitted to MFDS for the third, fourth and fifth year. The final report would be submitted in the sixth year refer to RMP milestone.	2 Sep 2019 2 Mar 2020 2 Sep 2020 2 Mar 2021 2 Mar 2022 2 Mar 2023 2 Mar 2024
MFDS re-examination report	2 Apr 2025

5. RATIONALE AND BACKGROUND

Acute lymphoblastic leukemia (ALL) is a rare, serious, and life-threatening condition with a need for improved therapies. Relapsed or refractory B-cell ALL is a fatal disease with a median survival time in adults of only approximately 3-6 months[1] [2]. The age adjusted incidence rate of ALL in the United States is 1.7 per 100,000 individuals per year[3], with approximately 6,020 new cases and 1,440 deaths estimated in 2014[4]. While the cure rates and survival outcomes for B-cell ALL have improved during the last several decades, most of the improvements have occurred in younger patients, primarily among children. Recent improvements are largely due to advances in the understanding of the molecular genetics and pathogenesis of B-cell ALL, incorporation of risk-adapted therapy and the advent of targeted agents.

CCI



Before the approval of BESPONSA® in Korea, this non-interventional study is designated as a Post-Marketing Surveillance (PMS) Study and is a commitment to Ministry of Food and Drug Safety (MFDS), as a part of Risk Management Plan (RMP) which is required by MFDS.

The safety and effectiveness information of BESPONSA® will be gathered at minimum 100 subjects administered in the setting of routine practice in Korea during the initial 6 years after the approval.

6. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are to determine any problems or questions associated with BESPONSA® after marketing, with regard to the following clauses under conditions of general clinical practice, in compliance with the regulation "Re-examination Guideline of New Drugs, Etc" (Ministry of Food and Drug Safety Notification 2015-79, 2015.10.30, amended).

(1) Serious adverse event/adverse drug reaction

(2) Unexpected adverse event/adverse drug reaction that has not been reflected in the approved drug label.

(3) Known adverse drug reaction

(4) Non-serious adverse drug reaction

(5) Other safety and effectiveness information

7. RESEARCH METHODS

7.1. Study design

This is a prospective, observational, non-interventional, multi-center study in which subjects will be administered as part of routine practice at Korean health care centers by accredited physicians. The study can be performed in Korean health care centers where BESPONSA® is prescribed to treat the relapsed or refractory B-cell precursor ALL.

7.2. Setting

All subjects enrolled should meet the usual prescribing criteria for BESPONSA® as per the local product document (LPD) and should be entered into the study at the physician's discretion.

7.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients diagnosed as relapsed or refractory B-cell precursor lymphoblastic leukemia (ALL).

2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

7.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Any patients who does not agree that Pfizer and companies working with Pfizer use his/her information.

2. Patients to whom BESPONSA® is contraindicated as per the local labeling.

7.2.3. Duration of the study

According to MFDS re-examination regulation, the re-examination report based on collected data of 6 years must be submitted to MFDS within 3 months after the end of specified re-examination period (from the product approval date to 6 years afterwards).

The data collection period of this study is until the required subject number (100 patients) is collected. The observation period for each subject is from initiating administration of first dose of BESPONSA® to the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a BESPONSA®. In case of patient that Hematopoietic Stem Cell Transplant (HSCT) after administrated BESPONSA®, follow-up until 180 days after transplantation. All the data collected during the observation period should be recorded in the case report form (CRF). In case of an adverse event/safety event recognized after the observation period ends, it should be recorded in the CRF as specified in Section 7.

7.2.4. Dosage and administration

The use and dosage recommendations for BESPONSA® should take place on the basis of the approved LPD. If subjects have been administered BESPONSA® off label, they should be excluded from the safety analysis set and analyzed separately.

Refer to the most updated LPD for the detailed information on prescription.

7.3. Study Procedures

7.3.1. Information of institution

The following will be recorded in the CRF for each patient:

- CRF number (Patient number): The investigator will sequentially assign each patient a patient identification number, which will be a 4-digit number. It will be combined with code number of institution by sponsor.
- Name of institution
- Name of department
- Name of investigator
- Date of signing data privacy statement
- Confirmation of Data Privacy Statement: If all agreement for using subject's personal and medical information, signature and date are obtained by subject or legally authorized representative, then check the box of "yes". If not, check "no" which means that case is excluded from this study.
- Confirmation of proper subject enrollment: If Subjects can be enrolled with satisfying the inclusion criteria, then check the box of "yes". If not, check "no" which means that case is excluded from this study.
- Signature of investigator: Contracted investigator must sign after identifying the CRF.

7.3.2. Subject information

- Date of birth
- Gender
- Height/Weight
- Pregnancy: If 'yes', then record the week of pregnancy.
- Breast-feeding
- Diagnosis: Select one among 'Philadelphia (+) B-cell ALL', 'Philadelphia (-) B-cell ALL', or 'Unknown'.
- First Diagnosis date/First treatment date: Record approximate date if an actual date is unknown.

- Current disease status: Select either 'refractory' or 'relapsed'. If 'relapsed', select one among 'first relapsed', 'second relapsed', or 'third or more relapsed'. Record the date of each onset. Record approximate date if an actual date is unknown.

7.3.3. Prior treatment history of B-cell precursor lymphoblastic leukemia

Prior to administrating BESPONSA®, if the subject received systemic therapy or hematopoietic cell transplant (HCT) to treat B-cell precursor lymphoblastic leukemia, record them. First, check among 'yes', 'no' or 'unknown'. If 'yes', record the followings.

7.3.3.1. Previous systemic therapy

- Regimen: Record the name of regimen.
- Purpose of treatment: Select one among 'induction', 'consolidation', 'maintenance', 'conditioning', or 'intensification'.
- Name of treatment drug: Record generic name.
- Duration of administration: Record the start date and stop date. Record approximate date if an actual date is unknown.
- Best response to therapy: First, check among 'conducted', 'not conducted' or 'unknown'. If 'conducted', record the date of evaluation and select one among 'complete response (CR)', 'CR with incomplete blood count recovery (CRi)', 'refractory disease', or 'progressive disease'. Response Criteria is defined according to *'NCCN Guideline Version 2.2016 Acute Lymphoblastic Leukemia*[9]*'*. Refer to Appendix 1 for detailed Response Criteria.

7.3.3.2. Previous Hematopoietic cell transplant

- Date of HCT: Record approximate date if an actual date is unknown.
- Best response to therapy: First, check among 'conducted', 'not conducted' or 'unknown'. If 'conducted', record the date of evaluation and select one among 'CR', 'CRi', 'refractory disease', or 'progressive disease'.

7.3.4. Medical History

Select among 'yes' or 'no' for medical history of followings. Past or present disease will be determined based on the first BESPONSA® administration date. Record adequate full name of the disease down as the Medical Terminology Dictionary indicates (written by Korean Medical Society).

7.3.4.1. Hepatic disorder / Renal disorder

If 'yes', record the name of the disease, severity and status.

Every subject must be evaluated whether he/she has ever had venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS). If he/she has, check 'yes' and select severity. Check 'no' if he/she had never had.

7.3.4.2. Allergic history

If 'yes', record the allergen and status.

7.3.4.3. Other diseases / symptoms

If 'yes', record the name of the disease and status.

7.3.5. Concomitant Medication

Record the concomitant medication including the transfusion while BESPONSA® is being administrated. First select either 'yes' or 'no' then record in more details if selected 'yes'.

- Name of medication: Record generic name.
- Treatment start date
- Treatment stop date: If the treatment is not terminated until the timing of CRF completion, leave it blank.
- Ongoing: If the treatment is not terminated until the timing of CRF completion, check 'ongoing'.
- Purpose of treatment: Select one among 'treatment for B-cell ALL', 'treatment for other diseases', 'treatment for an adverse event', 'prevention of drug side effect', or 'other'. If 'other', record the specific reason.

7.3.6. Administration status and response evaluation for each cycle of BESPONSA®

Record the following with regard to administrative status and response evaluation for each cycle. Record administrative status of all cycle until the last administration dose. Refer to LPD for posology and method of administration.

- Administration date

- Body surface area
- Administration dose
- Pre-medication: If 'conducted', record the detailed information in '4.Concomitant medication' clause in CRF.
- Response evaluation after each cycle: Record the evaluation date and response. Select one among 'CR', 'CRi', 'refractory disease', 'progressive disease', or 'relapsed disease'. Response Criteria is defined according to *'NCCN Guideline Version 2.2016 Acute Lymphoblastic Leukemia*[9]*'*. Refer to Appendix 1 for detailed Response Criteria. If response evaluation is not done, check 'undone' and leave the evaluation date blank.

7.3.7. Final effectiveness evaluation

Record the final effectiveness after all cycle of BESPONSA® is finished.

Check 'conducted' if final effectiveness is evaluated then record the date of evaluation. Check 'not conducted' if final effectiveness is not evaluated then select one reason why it is not conducted among 'death', 'follow up loss', or 'other'. If 'other', record the specific reason.

- Response criteria: Select one among 'CR', 'CRi', 'refractory disease', 'progressive disease', or 'Relapsed disease'.
- Plan for HCT: Check 'yes' if HCT is on plan or on ongoing for a subject.

7.3.8. Safety Evaluation

Safety will be assessed based on adverse events reported for all patients who received at least one dose of BESPONSA® and completed safety follow-up. Every observed and reported adverse event, regardless of the causal relationship with the study drug, must be recorded on an safety evaluation section in CRF

7.3.8.1. Definition of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant symptoms and signs;

- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

7.3.8.2. Definition of serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases

by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported:

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

7.3.8.3. Adverse events data collection

The investigator collects data on safety events as specified in Section 7 including all adverse events that occur during the observation period regardless of causal relationship to BESPONSA®. The information on adverse events should include the specific conditions or events, duration of the events (start date and stop date), severity, actions taken, seriousness (serious or non-serious), outcome and causal relationship to BESPONSA®.

Check either 'yes' or 'no' in adverse event occurrence section. If 'yes', record in detail.

- Adverse events: Record the name of adverse event. If possible, specify diagnosis, not individual symptoms. Record the name according to '*National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0*[10]'.

- Date of onset: Record the date of onset. Record approximate date if an actual date is unknown.
- Severity: Severity evaluation of AE must be done according to grades of '*NCI CTCAE Version 4.0*[10]'. If the severity of an AE changed, the AE must be entered separately. Record stop date of previous severity and onset date of new severity – along with completion of all other items.
- Action: Check relevant action of BESPONSA® dosage. Select one among 'withdrawn (temporarily or permanently, or delayed)', 'dose reduced', 'dose increased', 'does not changed', 'unknown', or 'not applicable'.
- Seriousness: Check either 'yes' or 'no'. If 'yes', record the appropriate number for the category of seriousness.

A serious adverse event is any untoward medical occurrence at any dose that:

① Results in death;

② Is life-threatening;

③ Requires inpatient hospitalization or prolongation of hospitalization;

④ Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

⑤ Results in congenital anomaly/birth defect.

⑥ Is important medical event (if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above)

Check the following at the end of the study or after the resolution of AE.

- Outcome: Check one among 'Recovered', 'Recovered with sequelae', 'Recovering', 'Not recovered' or 'Unknown' as a reply to a question; 'Is the AE still present?'. If the status has resolved, record the date of resolution. Record approximate date if an actual date is unknown.
- Causality of adverse event to the study drug: The causal relationship of adverse event to the study drug must be allocated by the physician according to the following criteria.

① Certain

- It follows a reasonable time sequence from administration of the drug (before and after the study medication).
- It could not be explained by other drugs, chemical substance or accompanying diseases.
- It has clinically reasonable reaction on cessation of the drug.
- It has pharmacological or phenomenological reaction to re-administration of the drug, where necessary.

② Probable/likely

- It follows a reasonable time sequence from administration of the drug (before and after the study medication).
- It could not be explained by other drugs, chemical substance or accompanying diseases.
- It has clinically reasonable reaction on cessation of the drug. (No information on re-administration)

③ Possible

- It follows a reasonable time sequence from administration of the drug.
- It could also be explained by other drugs, chemical substance or accompanying diseases.
- It lacks information or has unclear information on discontinuation of the drug.

④ Unlikely

- It is not likely to have a reasonable causal relationship from administration of the drug. Rather, it seems to be temporary.
- It could also be reasonably explained by other drugs, chemical substances or latent diseases.

* Other causality of adverse event: If the adverse event is not related to the study drug, physicians should indicate the most appropriate cause from the followings and record in detail.

(1) Disease under the study

(2) Other disease (please specify)

(3) Concomitant treatment drug or non-drug (please specify)

(4) Others (please specify)

⑤ Conditional/unclassified

- It needs more data to make an appropriate assessment or its additional data are being reviewed.

⑥ Unaccessible/unclassifiable

- Lack of sufficient information or conflicting information hampers accurate causality assessment or supplementation or confirmation.

7.4. Study Size

CCI [redacted]

CCI [redacted] [12, 13], and the adjustment application for the number of subjects, and 100 subjects will be collected during re-examination period. CCI [redacted]

7.5. Data Sources

In most cases, the source documents are the hospital's or the physician's patient chart.

7.6. Data management

CRF data collected by the investigator will be entered into the clinical database. Verifications will be performed after comparison of the double data entry. All missing data or data to be checked will be reported on a query sheet for further verification at the study site. Any data modification will be recorded.

7.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

7.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

7.7. Data analysis

Analysis will be performed for safety group and effectiveness group.

- Safety group: Subjects who have been administered BESPONSA® at least once and evaluated with safety-related endpoints at least once.
- Effectiveness group: Subjects who have been evaluated based upon effectiveness endpoints as described in this protocol.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

7.7.1. Safety analysis

- Safety parameter
  - Count and frequency of occurrence of adverse event, serious adverse event, adverse drug reaction or unexpected adverse event by category.
  - Count and frequency of occurrence of adverse events by subject baseline factor and by treatment factor to determine factors affecting the safety.
- Sub-analysis may be performed utilizing factors which are considered to affect safety. If required, chi-square test (X^2-test) will be used for subgroup analysis.

7.7.2. Effectiveness analysis

- Effectiveness parameter
  - Response after each cycle: CR, CRi, Refractory disease, Progressive disease, Relapsed disease
  - Final effectiveness: CR, CRi, Refractory disease, Progressive disease, Relapsed disease

- Effectiveness parameters will be descriptively summarized. If necessary, X^2-test, paired t-test, analysis by repeated measurement, and other statistical methods will be used.

7.7.3. Interim Analysis

As required by MFDS regulations, the periodic report should be submitted to MFDS every 6 months for the first two years and then annual report should be submitted to MFDS for the third, fourth and fifth year. The final report should be submitted in the sixth year. Interim analysis will be performed in time for the report submission.

7.8. Quality control

Quality assurance audits will be performed at study centers by the Pfizer's own independent quality assurance group or by clinical research organization. These audits will be conducted according to Pfizer's procedures and the guidelines for Good Pharmacoepidemiology Practices (GPP) (see Section 8.4).

7.9. Limitations of the research methods

This is a non-interventional PMS study conducted in the Republic of Korea to satisfy the requirements of MFDS. The protocol is determined by regulation of MFDS and not the specific disease and drug characteristics. The observational, non-controlled, and non-randomized design of this study has intrinsic limitations.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staffs have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

8.2. Patient consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator must ensure that each study patient, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative/parent(s) or legal guardian, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide

his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative, parent(s), or legal guardian and the patient's assent, when applicable, before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/IEC. The investigator will retain the original of each patient's signed consent document.

8.3. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol will be submitted to MFDS prior to the study. The ethical consideration on this study will be evaluated by IRB/IEC in each clinical site prior to the study if the site has an approval process for this PMS study according to the local standard operation procedure of the site.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer or its designee.

8.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices

described in Guidelines for GPP issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines, and Korea PMS regulations and/or guidelines.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1. Requirements

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up)

information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of BESPONSA®, or the time of the patient's data privacy statement if s/he is already exposed to BESPONSA®, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

Most often, the date of data privacy statement is the same as the date of enrollment. In some situations, there may be a lag between the dates of data privacy statement and enrollment. In these instances, if a patient provides data privacy statement but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to BESPONSA®, the SAE also must be reported to Pfizer Safety

9.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to BESPONSA®, follow-up by the

investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that BESPONSA® caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether BESPONSA® caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that BESPONSA® did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

9.4. Definitions of Safety Events

9.4.1. Adverse events

Refer to the '7.3.8.1. Definition of adverse events' clause.

9.4.2. Serious adverse events

Refer to the '7.3.8.2. Definition of serious adverse events (SAEs)' clause.

9.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) BESPONSA®, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to BESPONSA® (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to BESPONSA® prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to BESPONSA® during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with BESPONSA®, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to BESPONSA® in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;

- The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Lack of efficacy is defined as the failure of expected pharmacologic action or therapeutic benefit.

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Based on the "Safety Information Management Regulations for Drugs, Etc.", the staff in charge of safety information at Pfizer Korea reports to the Director of Korea Institute of Drug Safety and Risk Management via website, telephone, fax, mail or in the form of electronic document using Appendix Form no. 1 in the Safety Information Management Regulations for Drugs, Etc. (MFDS Notification) within 15 days of awareness or being notified of the serious adverse event/adverse drug reaction in accordance with Article 5 Paragraph 4 of the Re-examination Guideline of New Drugs, Etc (MFDS Notification no. 2015-79). Therefore, in case of a serious adverse event/adverse drug reaction, the investigator immediately notifies the staff in charge of safety information at Pfizer Korea. The investigator completes the 'Non-Interventional Study Adverse Event Report Form' and must fax it within 24 hours of awareness of the applicable serious adverse event/adverse drug reaction.

9.5. Single reference safety document

The latest version of the LPD of BESPONSA® will serve as the SRSD during the course of the study, which will be used by Pfizer to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For the first 2 years, 6-month reports will be submitted to MFDS (i.e., reports 1-1, 1-2, 2-1, and 2-2). Thereafter, data collected in the 3rd, 4th, and 5th year will be reported to MFDS annually. Final study report (i.e., re-examination report) will be submitted to MFDS in the 6th year to include all data collected during the whole study period.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

11. PUBLICATION OF STUDY RESULTS

Pfizer fulfils its commitment to publicly disclose study results through posting the results of this study on www.clinicaltrials.gov. Pfizer posts the results of all studies that is has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

- Basic Results are due within one anniversary year of the PCD and/or LSLV.
- When PCD and LSLV are not the same date, Basic Results are posted one anniversary year from the PCD and the record is updated one anniversary year from the LSLV. The PCD cannot occur after the LSLV.

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APPENDICES

APPENDIX 1. RESPONSE CRITERIA

APPENDIX 1. RESPONSE CRITERIA

Response Criteria is defined according to *'NCCN Guideline Version 2.2016 Acute Lymphoblastic Leukemia[9]'*.

The below outcome definitions will be used for reporting of response assessments.

Response Criteria for Blood and Bone Marrow:

- Complete response (CR)
  - No circulating blasts or extramedullary disease
    - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/central nervous system involvement
  - Trilineage hematopoiesis and < 5% blasts
  - Absolute neutrophil count (ANC) > 1000/microL
  - Platelets > 100,000/microL
  - No recurrence for 4 weeks

- CR with incomplete blood count recovery (CRi)
  - Meets all criteria for CR except platelet count and/or ANC

- Refractory disease
  - Failure to achieve CR at the end of induction

- Progressive disease
  - Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease

- Relapsed disease
  - Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR