"NON-INTERVENTIONAL (NI) STUDY PROTOCOL"

Study information

Title	A retrospective analysis of Inotuzumab ozogamicin (InO) usage in adult patients with relapsed/refractory (R/R) B-cell Acute Lymphoblastic leukemia (ALL)
Study Design	A multicentric retrospective cohort analysis of adult R/R B-cell ALL patients treated with Inotuzumab ozogamicin at tertiary care institutions.
Protocol number	B1931043
Protocol version identifier	Version 1.0
Date	14 November 2022
Active substance	Antineoplastic agents, other Antineoplastic agent, monoclonal antibodies, ATC code: L01XC26 Inotuzumab Ozogamicin
Medicinal product	Inotuzumab Ozogamicin
Research question and objectives	We aim to carry out a multicentric retrospective cohort analysis with data of approximately 55 patients treated with Inotuzumab ozogamicin monotherapy to provide clinical outcomes in real-world clinical practice in India.
Author	PPD

	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADC	antibody-drug conjugate
AE	adverse event
AEM	adverse event monitoring
allo-HCT	allogeneic hematopoietic stem cell transplantation
CNS	central nervous system
CR	complete remission
Cri	complete remission with incomplete hematologic recovery
CRF	case report form
DOR	duration of remission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HSCT	haematopoietic stem cell transplantation
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
InO	Inotuzumab ozogamicin
IQR	interquartile range
IRB	Institutional Review Board
MoAb	monoclonal antibody
MRD	minimal residual disease
NIS	non-interventional study
OS	overall survival

Ph	Philadelphia chromosome
R/R B cell ALL	Relapsed/Refractory/ B Cell Acute lymphoblastic leukemia
RFS	relapse free survival
SD	standard deviation
SDV	source data verification
SOS	sinusoidal obstruction syndrome
TKI	tyrosine kinase inhibitor
TRAE	treatment-related adverse event
US	United States
VOD	veno-occlusive disease
YRR	your reporting responsibilities

3. KEY DEFINITIONS

Index date: The date of initiation of the first cycle of InO.

Baseline period: Period from 6 months before index date to the index date. The closest observation recorded during the baseline period and closest to index date will be used as baseline data (when more than one observations are available).

CR/CRi rate: Number of patients who achieve complete remission/complete remission with incomplete hematologic recovery (CR/Cri) divided by the total number of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO).

Complete remission (CR): is defined as 5% bone marrow blasts, no evidence of disease in the bone marrow, and recovery of peripheral blood count (platelet count of > 100 x 109/L and absolute neutrophil count of > 1 x 109/L).

CR with incomplete count recovery (CRi): is defined as 5% bone marrow blasts and no evidence of disease in the bone marrow, but with incomplete recovery of peripheral blood count. Minimal residual disease (MRD) will be assessed at each participating institution by multicolor flow cytometry.

MRD negativity rate: Proportion of patients in whom minimal residual disease (MRD)-negative status is observed, among patients in whom MRD negativity status has been assessed, at any time until the end of treatment with InO (defined as the date of recorded discontinuation of InO).
OS: Time from index date to death.

RFS: Time from index date to the earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), or the start of new induction therapy or posttherapy haematopoietic stem cell transplantation (HSCT) without achieving CR/CRi.

EMD: Extramedullary disease is the presence of leukemic cell aggregates in the form of solid tumor outside that of bone marrow.[i]

LBL: lymphoblastic lymphoma, is a clonal hematopoietic stem cell disorder of B or T cell origin[ii]

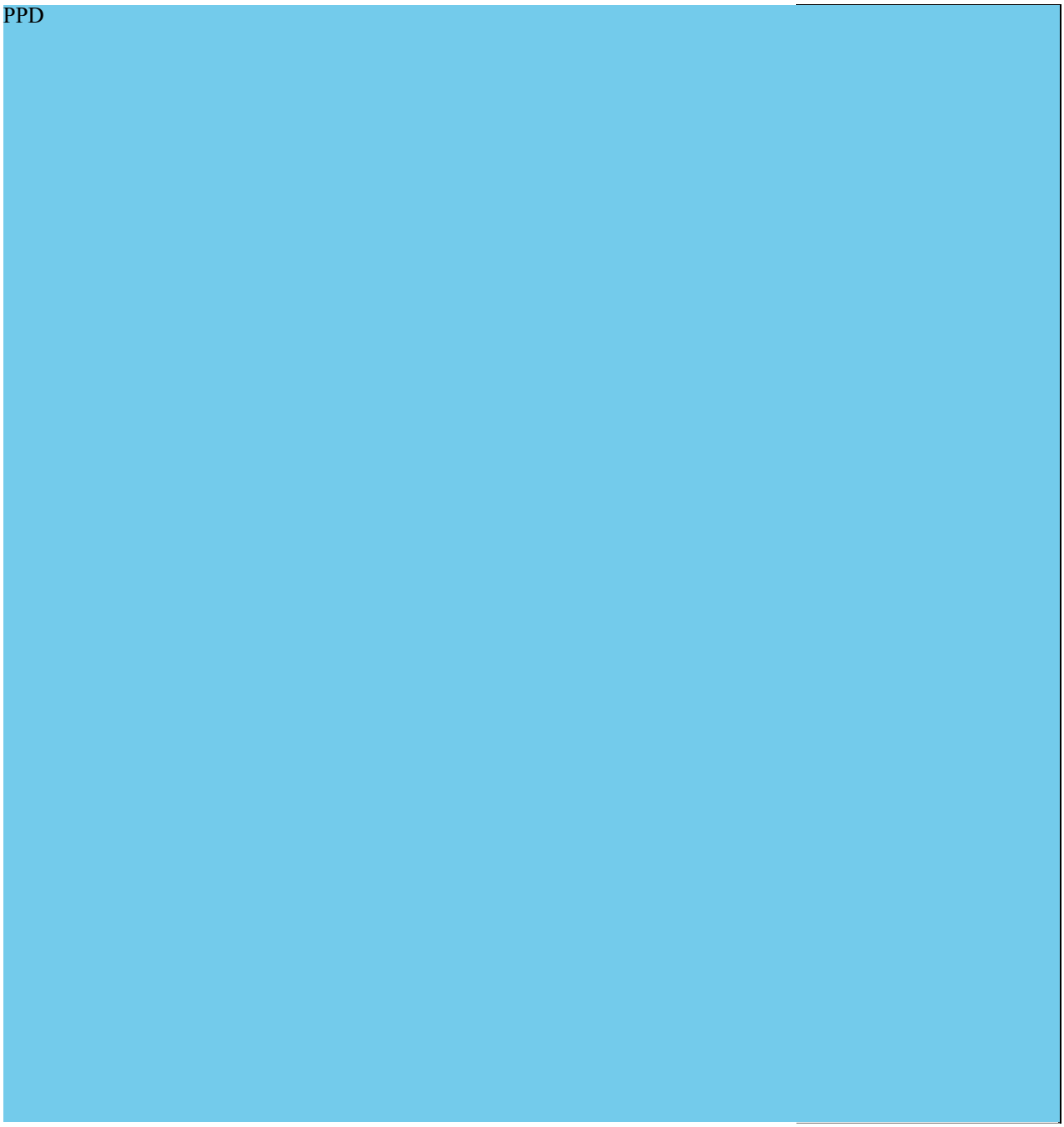
4. RESPONSIBLE PARTIES

Name	Job Title	Affiliation	E-Mail
PPD			

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD			

PPD



5. ABSTRACT

None

6. MILESTONES

Milestone	Planned date
Start of data collection	01 December 2022
End of data collection	28 March 2023
Final study report	15 June 2023

7. RATIONALE AND BACKGROUND

B-cell acute lymphoblastic leukemia (ALL) is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood,and extramedullary sites. Only 20% of ALL occurs in adult patients.[iii] Incidence data on adult B-cell ALL in India is lacking.[iv] The regimens used for pediatric patients with B-cell ALL are mostly used for the treatment of adult patients with B-cell ALL. The treatment of B-cell ALL in adults is mostly based on regimens developed for pediatric patients.

Most chemotherapy regimens used to treat adults with B-cell ALL in India consists of multi-agent induction, intensification or consolidation, and maintenance phases, together with central nervous system (CNS) prophylaxis using intrathecal chemotherapy, with or without cranial irradiation. Commonly used cytotoxic agents in first line treatment protocol for adult patients with B-cell ALL are cyclophosphamide, vincristine, daunorubicin, L-asparaginase and prednisolone. The prognosis of R/R B-cell ALL has historically been dismal with complete remission (CR) rates of 20-40%, median OS of 6 months, and cure rates of < 10% even with intensive salvage chemotherapy and HSCT[v].

R/R B-cell ALL in adults is a challenging disease, with high mortality resulting from refractory disease or toxicity from intensive chemotherapy regimens. The only curative option in this subset of patients is CR after salvage therapy followed by allo-HCT. Even salvage regimens in case of relapse are mostly composed of old agents used in first-line protocols. Although second remissions are possible, with these salvage regimes, these are of short duration unless an allogeneic stem cell transplant is feasible.[vi] The data on the outcomes of salvage therapy in adult patients with B-cell ALL is lacking from India. However, Novel therapies such as InO have improved the outcomes of this subset of patients, with more patients experiencing CR and minimal residual disease negativity, thus becoming eligible for allo-HCT. The real-world data on the use of Ino monotherapy in cases of adult R/R B cell ALL is limited in Indian settings with knowledge gaps relating to diagnostic and treatment practices. Currently, only a single study is available with CUP data from 8 patients.

InO is an antibody-drug conjugate consisting of a recombinant, humanized IgG4 antibody (G544) covalently bound to a semi synthetic derivative of calicheamicin. Calicheamicin, a cytotoxic natural product produced by microbial fermentation that is significantly more potent than conventional cytotoxic chemotherapeutic agents, binds to the DNA minor groove and causes cell death by inducing double strand DNA breaks. The targeting agent in InO, (G544) specifically recognizes human CD22, which is expressed on the malignant cells of the majority of B-lymphocyte malignancies, including on the surface of blasts in >90% of patients with B cell ALL.[vii] In 2017, the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved InO for the treatment of adult with R/R B-cell precursor B-cell ALL.[viii,ix]

Inotuzumab: mode of action and literature evidence

ALL is the second most common acute leukemia in adults. The characteristic features are chromosomal abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells. The backbone of therapy remains multi-agent chemotherapy with

vincristine, corticosteroids and an anthracycline with allogeneic stem cell transplantation for eligible candidates.[x]

The advent of moAb targeting CD22 (InO) and CD19 (blinatumomab), have dramatically improved the outcome of adults with R/R B cell ALL. These have shown significant survival benefits against standard therapies and expanded the armamentarium of ALL.[xi]

InO is an anti-CD22 moAb conjugated to the cytotoxic antibiotic calicheamicin. Based on promising phase I/II data, InO was compared to standard salvage chemotherapy in Phase 3 multicenter trial (INO-VATE) of 218 adult patients with CD22+ B cell ALL. The overall response and MRD negativity rates among responders were significantly higher with InO compared with chemotherapy (81% versus 29%, $p < 0.001$, and 78% versus 28%, $p < 0.001$, respectively). More patients who received InO were able to undergo HSCT (41% versus 11%; $p < 0.001$). The median remission duration and progression-free survival were significantly longer with InO (4.6 versus 3.1 months; $p = 0.03$, and 5.0 versus 1.8 months; $p < 0.001$, respectively). The median OS was 7.7 versus 6.7 months ($p = 0.04$). This was later confirmed with longer follow-up on 326 patients showing 2-year OS rates of 23% versus 10% ($p = 0.01$) in favor of InO [24]. Predictors for better survival included achievement of CR, MRD negativity, and consolidative HSCT. Patients who achieved MRD negativity derived more benefits regardless of the number of prior therapies.[xii]

InO is an ADC comprising of a moAb targeting CD22,[xiii] a cell surface antigen expressed on approximately 90% of B-cell malignancies,[xiv] linked to a cytotoxic agent.

CD22 is an important modulator of B-cell lymphocyte function and survival,[xv] and is expressed on mature B-cells, which may allow for targeted delivery of the cytotoxic agent.[xvi]

When InO binds to the CD22 antigen on malignant B-cells, it is absorbed into the cell, at which point the cytotoxic agent calicheamicin is released to destroy the cell.[xvii]

Adding an ADC targeting CD22, such as InO, to existing treatments options, may provide additional anti-tumor activity.[xviii]

8. RESEARCH QUESTION AND OBJECTIVES

We aim to carry out a multicentric retrospective cohort analysis study with data from approximately 55 patients to observe clinical outcomes among patients treated with InO monotherapy in real-world clinical practice in India.

9. RESEARCH METHODS

This research is designed as a multicenter, retrospective study. Site investigators, namely hematologists /oncologists who are experienced in treating hematological malignancies in India will drive this research.

9.1. Study design /Setting

The study is classified as a Non-interventional study (NIS) secondary data collection- unstructured review with sites/investigators.
R/R B-cell ALL patients who are 18 years old at the time of InO initiation and those who received the drug outside of clinical trials will be evaluated.

Data will be collected retrospectively from patients hospital medical records (paper-based) by members of the direct care team (investigators). We intend to have 7- 10 sites across India using InO monotherapy including patients with both private purchase and compassionate use to reach a cohort of approximately 55. If needed, more sites will be enrolled to meet the target cohort. Data will be reviewed and analyzed from all the sites.

Medical records will be reviewed to collect demographic, patient-related, disease-related, and clinical outcome data. These patients will be evaluated for response (CR/CRi), MRD status, duration of remission (DOR), Dosage patterns, Rate of transplant, Overall survival in all patients including Survival rate at 6 months and 12 months in transplanted patients & non transplanted patients, Relapse free survival (RFS), Rate of VOD (Total, during study treatment and post HSCT if any patient underwent HSCT), safety/tolerability, Other adverse effects (including hematological toxicities and raised liver enzymes), No of cycles to achieve MRD negativity in responders & CR/CRi in EMD/LBL.

9.1.1. Inclusion criteria

- Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:
- Patient Population -
- Patients aged ≥18 years old at the initiation of InO treatment
- Patients with relapsed/refractory B-cell ALL
- Patients who initiated InO monotherapy between Feb’2017 and Feb’2022 and are CD22 positive
- Ph+ patients who have failed treatment with at least 1 TKI

9.1.2. Exclusion criteria

- Patient not completing at least 1 cycle of InO therapy
- Patient on InO in combination with chemotherapy

Following local legislation, informed consent won't be signed by the patients since this is a retrospective study and they are not getting enrolled in a prospective clinical trial. All data points mentioned in the inclusion criteria should be available which are necessary to analyze protocol endpoints for the selected patient cohort who has undergone the full treatment of the drug in question. Ethics Committee approval of study protocol will be taken to access medical records.

9.1.3. Primary endpoint

Complete remission or complete remission with incomplete hematological recovery following treatment with InO, by the number of salvage therapies (0, 1, ≥2) received before InO initiation.

9.1.4. Secondary endpoints

- MRD Negativity following initiation of Ino
- Number of cycles of InO needed to attain CR/CRi
- DOR
- Dosage pattern: InO doses, dose modifications, and the number of cycles of treatment;
- Concomitant medications
- Rate of transplant (No of patients who proceeded to transplant)
- Survival rate at 6 months & 12 months (transplanted patients & non transplanted patients, in both who achieved CR/CRi and MRD negativity)
- Cause of death
- Relapse-free-survival; in all patients and patients with or without follow-up HSCT.
- Rate of VOD (Total, during study treatment and post HSCT, if any patient underwent HSCT) in transplanted & non transplanted patients.
- Occurrence of Grade 3/4 treatment-related adverse events in lung/cardiac/kidney/liver etc following InO initiation; in all patients and patients with or without follow-up HSCT & hematological toxicities
- CR/CRi in EMD/LBL

All these parameters will be assessed in the following subgroups –

- 1st salvage and later lines
- High burden and Low burden disease (<50%; 50-90%; >90%)
- Ph +ve and Ph – ve patients
- Elderly patients> 65 years

9.2. Data sources

Data for this study will be collected through retrospective data collection from 7-10 sites for patients in India who received Inotuzumab for the indication of adult R/R B Cell ALL between the time period Feb'2017 – Feb'2022. Additional centers may be added at a later stage if the target sample size is not achieved.

Data will be collected in anonymized form on Paper/excel based CRF for the study. Participants will be identified in all study records by a unique participant identification number to allow data management queries to be resolved with reference to source medical records while preserving patient confidentiality.
Medical records will be reviewed from secondary data sources to collect demographic, patient-related, disease-related, and clinical outcome data & AE's. These patients will be evaluated for response, duration of response (DOR), OS from the time of InO initiation till 6 months or 1 year of therapy and toxicity
Data to be verified in accordance with Protocol standards. Before obtaining the data from the selected sites across the nation, the necessary regulatory approval will be ensured.

9.3. Study size

This is a descriptive study and there is no prior hypothesis specified, therefore a formal power calculation is not required. The sample size of approximately 55 patients has been based on the number of patients expected to be available at these 7-10 sites that individually treated the largest number of patients with InO
The study will include information on approximately 55 patients as per the availability of data from 7-10 sites.

9.4. Data management

9.4.1. Collection, Monitoring, Processing of Data and Archiving:

Data pertaining to all fields required to fulfill the primary and secondary endpoints of the study will be captured in a paper Case Report Form (CRF). Data from the paper CRF will then be transferred to an excel master managed by Insignia. Data entry, data query generation & resolution, source document verification & database lock will be performed as per standard GCP guidelines.

Rules for completing CRFs

Print legibly using preferably a black/blue ballpoint pen. Ensure that all questions are answered and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks.
If the question is irrelevant (eg, is not applicable) indicate this by writing "NA" (not applicable) in the respective ensure that all information derived from source documentation is consistent with the source information. By signing the affirmation statement, the Investigator confirms that the information answer field.
The investigator staff must is complete and correct.

Corrections to CRFs:

Corrections to the data on the CRFs must only be made by drawing a straight line through the incorrect data and by writing the correct value next to data that has been crossed out. Each correction must be initialed, dated and explained by the Investigator or the Investigator's authorised staff.

Monitoring of CRFs:

Filled case report forms will be checked for accuracy by designated staff before sending them to Insignia for data entry, validation and analysis. The case report forms will be checked and collected in a mutually agreed frequency. Investigator will be responsible for the retention of patient notes for 1 year from the study closeout

9.4.2. Case report forms (CRFs)/Data collection tools (DCTs)

As used in this protocol, the term CRF should be understood paper-based case report form for 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 paper case report 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.

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

9.4.3. 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), 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 as 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 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 Insignia Communications Pvt Ltd and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 5 years or as required by applicable local regulations.
The investigator & Insignia Communications must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.5. Data analysis

All qualitative outcomes will be summarized by frequency and percentage. The quantitative outcome will be summarized by mean and SD if data is symmetric, otherwise median, and IQR. The outcomes will also be classified and compared across different demographic and relevant clinical factors. External validity will be assessed by t-test/ANOVA or chi-square test of indepdence depending on the nature of the outcome. However, observations will be generalized for the population the selected patients would represent. p-value<0.05 will be considered statistical significance. A standard statistical software will be used for data analysis.

9.6. Quality control

9.6.1. Monitoring and Quality Control:

Insignia representative or delegate will:
Establish the adequacy of the facilities and the investigator's capability to appropriately select the sample.
Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol compliance, and the responsibilities of Insignia or its representatives.
During the study, the Insignia representative or delegate can implement different activities to assure compliance with Insignia's standards of quality. These activities could include but are not limited to:

Contacts with the sites to:
Provide information and support to the investigator(s).
Ensure that the research team is complying with the protocol and that data are being accurately recorded in the CRFs.
Ensure that the CRFs are completed properly and with adequate quality.
Post-entry pre-analysis data validation will be performed, and if any information is missing or incorrect, the sites will be contacted.
Monitoring activities for:
Checking that patients exist in medical records (a sample)
The extent and nature of monitoring will be mutually decided. If the study in charge is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

9.6.2. Reporting and Publication of Data:

Insignia will prepare a Study report within 2 months after the completion of the last patient.
If a report of the study is published, the contribution of participating doctors will be duly acknowledged.
Insignia is obliged to analyze and report all study data as described in the protocol.
In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of the study, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available.
Insignia endeavors to publish the results of study and is committed to ensure that the data are reported in a responsible and coherent manner.
Insignia seeks to ensure that publications in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals.
Insignia is committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "Each author should have participated sufficiently in the work to take public responsibility for the content."

9.7. Limitations of the research methods

- The medical records may not be available for each & every data points provided in the CRF, from the aspect of the clinician or the patient.

- Patients may be lost to follow-up due to the occurrence of AEs, lack of efficacy or other reasons.

- This could be due to censoring events, that is, information on time to outcome event may not available for all study participants. Patient/s in such cases will be marked as "censored" when such information on time to event is not available due to loss to follow-up or non-occurrence of outcome events before the end of the study.

- For such patients (censored because of lost to follow-up due to the occurrence of AEs, lack of efficacy or other reasons), the use of Kaplan-Meier curves will be obtained as estimates of median OS, RFS and time to CR/Cri taking into account patients' attrition.

- The interpretation of data collected retrospectively will be dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from the medical records. However, Source data verification (SDV) will be employed to identify and correct abstraction errors.

10. PROTECTION OF HUMAN SUBJECTS

In this retrospective study, the anonymity of patients is of utmost importance. Several measures are taken to ensure the confidentiality of the collected information. Reviewers, monitors and data analysts are under a confidentiality agreement with the CRO to maintain the secrecy of the

information. Study personnel would never contact individual patients or physicians. During the data collection, the records would never be left unattended and will always be stored in a locked room. Approval from the institutional review board and ethics committee, the custodians of patient data privacy, will be obtained.

Patient identifiers will be kept in a dataset separately from the primary database.

10.1. PATIENT INFORMATION

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure the 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 e-CRF excel form and will be password protected or secured in a locked room to ensure that only authorized study staff has access. The study site will implement appropriate technical and organizational measures to ensure that personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has occurred and, if so, providing breach notifications as required by law.

- To protect the rights and freedoms of natural persons concerning 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.

10.2. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

IRBs/IEC review and approval for each site will be obtained for access to anonymized patient medical records.

10.3. Ethical conduct of the study

The study will be performed following ethical principles that are consistent with the Declaration of Helsinki, ICH GCP, ICMR, and the applicable legislations. The Investigator will perform the study in accordance with the regulations and guidelines governing medical practice and ethics in the country

of the study and in accordance with currently acceptable techniques and know-how and in accordance to the below mentioned guidelines.

1. Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety
2. Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
3. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making
4. European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
5. FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

- All AEs will be captured from the medical records.

- Number of Participants Who Experienced a Documented Diagnosis of Veno-occlusive Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS) Post InO Treatment.

- Number of Participants Who Survived Following Treatment For Documented Diagnoses of Veno-occlusive Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS).

- Number of Participants With Interrupted InO Treatment Due to VOD/SOS.

- Number of Participants Who Experienced Grade 3 and Grade 4 (Lung/Cardiac/Kidney/Liver) Treatment-Related Adverse Event (TRAE) Following InO initiation.

- All hematological AEs: Neutropenia, febrile neutropenia, and thrombocytopenia

- Being NIS secondary data collection– This study involves retrospective patients treated with InO for R/RB-cell ALL data that exist as unstructured data by the time of study start or a combination of existing unstructured data, which will be converted to structured form during the implementation of the protocol solely in an excel using CRF template.

- It is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. SAFETY REPORTING

- This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

- The requirements for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

    - All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the case report form & AE reporting form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

    - Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

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

    - For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

‘‘All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

- All research staff members must complete the following Pfizer training requirements:

“Your Reporting Responsibilities (YRR) Training for Vendors.’’

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a “Confirmation of Training Certificate” (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, 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.

14. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

15. REFERENCES:

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[iv] Samra B, Jabbour E, Ravandi F, Kantarjian H, Short NJ. Evolving therapy of adult acute lymphoblastic leukemia: state-of-the-art treatment and future directions. *J Hematol Oncol*. 2020;13(1):70.

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Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	24-Nov-2022 11:15:36	Manager Approval

15 May 2024

RE: Protocol Administrative Changes and Clarifications for Study B1931043: A Retrospective analysis of Inotuzumab ozogamicin usage in adult patients with relapsed/refractory (R/R) B-cell Acute Lymphoblastic leukemia (ALL)

Dear Healthcare Provider/Investigator,

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes and clarifications to the B1931043 protocol Version 1 and Version date 14 Nov 2022. The edit described below clarify inconsistencies in the text of the protocol and provide administrative changes. The planned changes is not considered substantial by Pfizer Inc because there is no significant impact to the safety or physical or mental integrity of the study participants, the scientific value of the study, the conduct or management of the study, and therefore *are* not part of a formal amendment.

This PACL makes the following changes:

No.	Serial numbers as per Protocol	Rationale for the changes	Updated details
1	**4.** RESPONSIBLE PARTIES Principal Investigator(s) of the Protocol	3 sites were withdrawn from the study	Deletion of the following investigators PPD
2	4. RESPONSIBLE PARTIES Principal Investigator(s) of the Protocol	1 site was added to the study	PPD

3	6. MILESTONES	Change in Milestones- Planned Date	Start of data collection - 13 February 2023 End of data collection - 05 July 2023 Final Study report - 10 October 2023
4	9. RESEARCH METHODS 9.3 Study size	Sample size changed to 32 subjects	Sample size is changed to 32 subjects
5	11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 12. SAFETY REPORTING	To clarify the adverse event reporting requirements for structured and unstructured data components. Also, to correct the inconsistency with the protocol template language.	The last 2 paragraphs of Section 11 should be moved to the beginning of Section 12, Adding a subheading "12.1 Structured Data Analysis", under which the 2 paragraphs are pasted and revised. In addition, add a second sub-heading "12.2 Human Review of Unstructured Data" above the original content of Section 12.

In the event that this protocol requires substantial changes that apply globally to all sites in the future or regulatory authorities request that these changes be incorporated into an updated protocol, the administrative changes described in this letter will be incorporated into the amended protocol.

Please inform your institutional review board/ ethics committee of these changes, as required.

Sincerely,
Dr. PPD

cc: NI study master file

PPD

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