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CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Multicenter, Open-label Study of IMGN632 Monotherapy Administered Intravenously in Patients with CD123-positive Acute Myeloid Leukemia and Other CD123-positive Hematologic Malignancies
Study Number	IMGN632-0801
Study Phase:	1/2
Product Name:	IMGN632
Regulatory Agency Identifier Numbers	IND Number: 130889 EU CT Number: 2024-514195-40-00
Indication:	Acute myeloid leukemia, blastic plasmacytoid dendritic cell neoplasm, acute lymphoblastic leukemia, myelodysplastic syndrome, myeloproliferative neoplasms, hematologic malignancies
Sponsor:	ImmunoGen, Inc. (now a part of AbbVie, Inc.) 830 Winter Street Waltham, MA 02451, USA
Sponsor Contact:	[redacted], MD, MPH [redacted] Oncology Clinical Development Phone: [redacted] Email: [redacted]
Original Protocol Date (Version 1.0): Version 1.1 Date: Version 2.0 Date: Version 3.0 Date: Version 4.0 Date: Version 5.0 Date: Version 6.0 Date: Version 7.0 Date: Version 8.0 Date: Version 9.0 Date: Version 10.0 Date:	07 August 2017 05 September 2017 09 October 2017 13 October 2017 29 June 2018 15 November 2019 04 February 2021 07 January 2022 21 October 2022 30 May 2023 20 November 2024

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SPONSOR SIGNATURE PAGE

[redacted]

[redacted]

[redacted], MD, MPH
[redacted]
Oncology Clinical Development
Phone: [redacted]
Email: [redacted]

INVESTIGATOR'S AGREEMENT

I have read the IMGN632-0801 Protocol and agree to conduct the study as outlined and in conformance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of the Investigator

_____

Site Name

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Contact Information
[redacted]	[redacted], MD, MPH	Phone: [redacted] Email:

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ImmunoGen, Inc. (now a part of AbbVie, Inc.)

Name of investigational product: IMGN632

Description of IMGN632: IMGN632 is an antibody-drug conjugate consisting of an anti-CD123 monoclonal immunoglobulin G1 (IgG1) antibody (G4723A) attached via a succinimide linkage to the DGN549-C linker-payload, which consists of the FGN849 payload (active moiety) and peptide linker change. IMGN632 binds to CD123+ cells and, upon intracellular processing, releases a highly potent and cell membrane-permeable payload, FGN849. FGN849 is a member of the novel indolinobenzodiazepine pseudodimer (IGN) class of cytotoxic molecules that bind to the minor groove of DNA, leading to DNA alkylation, apoptosis, and cell death.

Title of study: A Phase 1/2, Multicenter, Open-label Study of IMGN632 Monotherapy Administered Intravenously in Patients with CD123-positive Acute Myeloid Leukemia and Other CD123-positive Hematologic Malignancies

Study center(s): Approximately 20 centers in the US and Europe

Lead Investigator: [redacted], MD (MD Anderson Cancer Center)

Study period (months): Approximately 51 months (including follow-up)	**Phase of development:** Phase 1/2

Rationale: CD123 is the alpha subunit of the interleukin-3 receptor (IL-3Rα). CD123 expression is low on normal hematopoietic stem cells (Testa 2014). However, CD123 is overexpressed in multiple hematologic malignancies of both myeloid and lymphoid origins, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), B-cell acute lymphoblastic leukemia (B-ALL), chronic myeloid leukemia in blast crisis/phase (BP-CML), and blastic plasmacytoid dendritic cell neoplasm (BPDCN) (Testa 2014).

IL-3 is produced by activated T lymphocytes. IL-3 together with other growth factors stimulates the development and mediates the survival of a wide range of hematopoietic cells in bone marrow (Testa 2014). CD123 levels on normal hematopoietic stem cells are very low, but early common myeloid progenitors express higher CD123 levels (Testa 2014, Jordan 2000). Medium to high expression of CD123 on normal tissues is limited to rare populations of white blood cells, such as plasmacytoid dendritic cells and basophils (Jordan 2000, Testa 2014).

Preliminary toxicity studies in rodents and monkeys with IMGN632 and FGN849 (the active catabolite) demonstrate that the toxicity is limited primarily to the gastrointestinal tract and cytopenias. Based on preclinical toxicity and anti-AML efficacy, the data suggest a wide therapeutic index in mice and a 150-fold differential cytotoxicity of human leukemic cells to normal hematopoietic progenitors, predicting a favorable clinical profile.

AML is the most common form of acute leukemia among adults and accounts for the largest number of deaths from leukemias in the United States (US) (SEER 2018) and Europe. It is estimated that approximately 40,000 people in the US and Europe are diagnosed with AML per year, with 50% of patients dying from the disease (Siegel 2016). The median age of diagnosis is 66 years. Frontline chemotherapy in AML is reported to induce complete response/remission (CR) in 70% to 80% of patients who are 60 years of age or younger and in approximately 50% of older patients. “Fit” patients are judged to be able to tolerate intense treatment, are often younger (< 60 years), and typically receive 1 to 2 cycles of induction with “7 + 3,” a combination of cytarabine and anthracycline, typically daunorubicin. Following this, these fit patients may receive high dose cytarabine for 1 or more cycles and may receive a stem cell transplant. Standard induction and post-induction therapies result in a

median duration of remission of approximately 1 year and potential cures in 25% to 35% of the patients. “Unfit” patients, often older, typically receive azacitidine, a hypomethylating agent, with or without venetoclax. Approximately 30% to 60% of these patients will obtain a complete remission. However, most AML patients are refractory to treatment or will relapse, and AML salvage regimens offer poor outcomes with significant toxicity. Thus, novel therapies with limited toxicity in this relapsed population are needed, and such patients represent an appropriate population for an initial IMGN632 therapeutic trial.

BPDCN is a rare, aggressive hematologic malignancy derived from myeloid dendritic cell precursors, which often manifests with skin lesions in addition to lymph node, blood, and bone marrow involvement. Characterized by CD4, CD56, and CD123 expression among other markers, BPDCN blasts express high levels of CD123 and thus represent an appropriate patient population for anti-CD123-targeted therapy. Intense chemotherapy and tagraxofusp-erzs (ELZONRIS) are standard-of-care treatment options in Europe and the US. CR rates of 47% to 86% in frontline disease, and median overall survival (OS) of 12 to 24 months are seen with these therapies. However, the majority of BPDCN patients will eventually relapse with no effective salvage treatment options; therefore, BPDCN represents a disease with a high unmet need.

ALL is a rare, aggressive hematologic malignancy derived from lymphoid precursors, which often manifests with lymph node, blood, and bone marrow involvement. B-cell acute lymphoblastic leukemia and some T-cell acute lymphoblastic leukemia blasts express CD123 at levels similar to AML blasts and thus represent an appropriate patient population for anti-CD123-targeted therapy. Initial remission rates are high, and long-term survival rates are 68% overall (SEER 2018). Although patients with relapsed ALL have chemotherapeutic and immunotherapy options, long-term survival has been < 25% for these patients (Frey 2015); therefore, relapsed/refractory ALL patients represent an appropriate population for an initial IMGN632 therapeutic trial.

Objectives:

Dose Escalation and AML/ALL/Other Expansion Phase

Primary objective

- To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of IMGN632

Secondary objectives

- To characterize the safety profile and tolerability of IMGN632 when given as a single agent across dose levels and schedules
- To characterize the pharmacokinetics (PK) of IMGN632, total antibody, and FGN849 (active catabolite)
- To evaluate the potential immunogenicity of IMGN632
- To assess the antileukemia activity in AML, ALL, and other patients (tumor-specific expansion cohorts)

Exploratory objectives

- To characterize the pharmacodynamic (Pd) profile of IMGN632, by assessing target saturation by IMGN632 and persistence of saturation, during the dose escalation portion of the study

[redacted]

[redacted]

BPDCN Expansion Phase (Cohorts 1 and 6)

Primary objective

- To assess the rate of composite CR (CCR) in frontline de novo BPDCN patients in Cohort 6: CR+clinical CR (CRc)

Secondary objectives

- To assess the rate of CCR: CR+CRc
- To assess the duration of CCR (DOCR) in frontline de novo BPDCN patients in Cohort 6: CR+CRc
- To assess the DOCR for relapsed/refractory and other frontline patients with CR or CRc in Cohorts 1 and 6
- To characterize the safety profile and tolerability of IMGN632 when given as a single agent at the RP2D level
- To assess the rate of CR+CRc+CRh (CR with partial hematologic recovery)
- To assess the duration of CR+CRc+CRh
- To assess the overall response rate (ORR): CR+CRc+CRh+CRi (CR with incomplete recovery)+partial response (PR)
- To assess the duration of overall response (DOR)
- To assess OS
- To assess the percent of BPDCN patients able to bridge to stem cell transplant in the frontline and relapsed/refractory populations separately
- To characterize the PK of IMGN632, total antibody, and FGN849 (the active catabolite)
- To evaluate the potential immunogenicity of IMGN632
- To assess transfusion independence

Study design overview:

This is an open-label, multicenter, Phase 1/2 study to determine the MTD, RP2D if different, and recommended dosing schedule for IMGN632 monotherapy and to assess the safety, tolerability, PK, immunogenicity, and antileukemia activity of IMGN632 when administered to patients with CD123+ malignancies.

This study includes a Dose Escalation Phase followed by a Dose Expansion Phase.

The Dose Escalation Phase will establish the MTD(s) for IMGN632 when given on different schedules and will explore the safety profile and antileukemia activity at selected RP2Ds and recommended schedule(s). The Dose Expansion Phase will include treatment with IMGN632 at different dose levels and schedules in different disease populations.

This clinical study will be conducted in compliance with the protocol, International Conference on Harmonisation E6 Good Clinical Practice, and the applicable regulatory requirement(s).

Dose Escalation and AML/ALL Expansion Phase

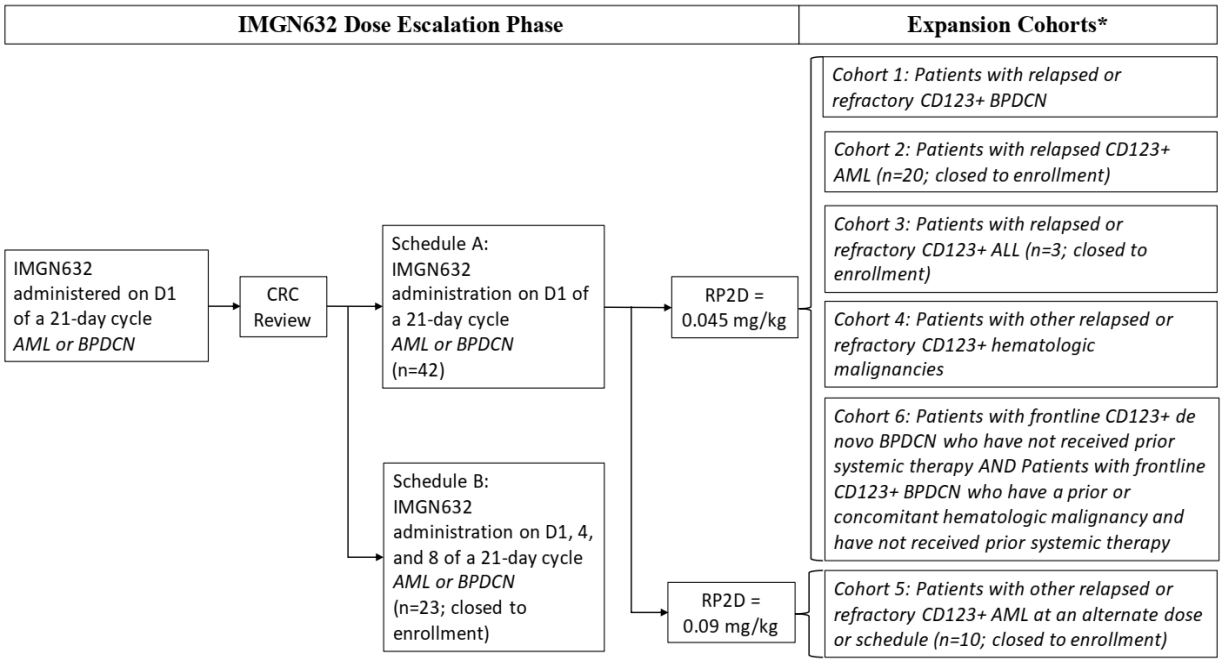
For dose escalation, eligible patients will be ≥ 18 years of age and will have relapsed/refractory CD123+ AML or BPDCN. The Dose Escalation Phase will follow a standard 3 + 3 cohort design. Two dosing schedules may be evaluated in this portion of the study:

- Schedule A: IMGN632 administered on Day 1 of a 21-day cycle
  - The starting dose for IMGN632 will be 0.015 mg/kg (Section 1.3). The dose escalation regimen ranges from 3-fold with the first dose escalation to 1.5-fold with the last dose escalation. The rationale for the 3-fold increase in dose between Cohort 1 and Cohort 2 is based upon the use of a non-cross-reactive toxicology species to determine the no observed adverse effect level (NOAEL) and the increased clearance of IMGN632 predicted in patients based on interspecies scaling.
- Schedule B: IMGN632 administered on an alternate dosing schedule (Days 1, 4, and 8 of a 21-day cycle) (closed to enrollment)
  - The maximum starting dose for Schedule B will be determined by the cohort review committee (CRC) based on available safety, Pd, and PK data from the last dose cleared on Schedule A or lower doses based on PK and CD123 saturation kinetics. IMGN632 will be administered in equal fractions across Days 1, 4, and 8 of a 21-day cycle (eg, 1/3 of the total dose administered on Schedule A on each of Days 1, 4, and 8).

Study enrollment opened with IMGN632 being administered on Schedule A and explored escalating doses of IMGN632 based on a modified Fibonacci escalation schema (Table 2). Patients were enrolled into cohorts using a standard 3 + 3 design. During the escalation phase, a total of 65 patients were enrolled, 42 under Schedule A and 23 under Schedule B. Based on nonclinical pharmacology, clinical safety, PK, and Pd assessments during the Dose Escalation Phase of the study, a dose of 0.045 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohorts 1, 2, 3, 4, and 6, and a dose of 0.09 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohort 5. Schedule B is no longer being explored (see Study design schema).

The MTD for a given schedule is defined as the highest dose at which < 2 of 6 patients experience a dose-limiting toxicity (DLT) in a dose cohort. Based on input from the CRC review of data, including PK, Pd, safety, and any signs of activity, up to 12 patients in total at a given dose level (at or below the MTD) may be enrolled to further characterize safety and identify the true DLT rate in addition to characterizing efficacy signals.

Study design schema



*Dose expansion cohorts were planned in patient populations as described by Cohorts 1 through 6. Cohort 1 will enroll approximately [redacted] relapsed or refractory BPDCN patients. Up to [redacted] frontline CD123+ BPDCN patients who have not received prior systemic therapy are planned to be enrolled in Cohort 6 (up to [redacted] patients with de novo BPDCN and up to [redacted] patients with BPDCN who have a prior or concomitant hematologic malignancy). Enrollment in Cohort 4 is planned for up to [redacted] patients. Enrollment in Cohorts 2, 3, and 5 is closed.

Planned dose escalation cohorts – Schedule A

Dose Escalation Cohorts	IMGN632 (mg/kg/dose)	Fold Dose Increase Over Prior Dose Level
1	0.015	--
2	0.045	3
3	0.09	2
4	0.18	2
5	0.3	1.67
6	0.45	1.5
7	0.67	1.5
8	1.0	1.5

Dose expansion cohorts: The 2 cohorts in AML (Cohort 2 and Cohort 5, closed to enrollment) explored differences in efficacy and safety between 2 doses on 2 different schedules to aid in the design of Phase 2 and combination studies. Cohort 3 (closed to enrollment) investigated efficacy and safety in patients with relapsed or refractory CD123+ ALL.

The monitoring of DLTs across all cohorts at the same dose level will use a frequentist approach using a maximum probability of DLT of 20% as stopping rule (Section 3.3.4).

BPDCN Expansion Phase

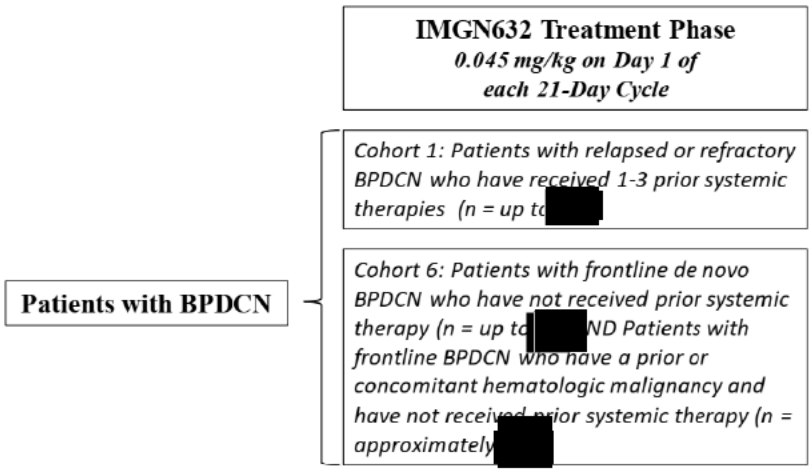
Patients with BPDCN will be enrolled into 1 of the following cohorts:

- Cohort 1: Patients with relapsed or refractory BPDCN who have received 1 to 3 prior systemic therapies (including tagraxofusp-erzs and any other systemic therapy deemed appropriate for the treatment of BPDCN)
- Cohort 6: Patients with frontline de novo BPDCN who have not received prior systemic therapy and patients with frontline BPDCN who have a prior or concomitant hematologic malignancy (PCHM) and have not received prior systemic therapy

All patients will receive the RP2D of 0.045 mg/kg IMGN632 by intravenous (IV) infusion on Day 1 of a 21-day cycle. All 3 areas of potential disease involvement (skin, bone marrow, nodal/visceral) will be assessed to establish a response; subsequently repeated computed tomography/positron emission tomography (CT/PET) scans will only be performed on patients with nodal/visceral disease at baseline, or as indicated clinically. Bone marrow and skin assessments will continue per schedule for all patients.

PK will be evaluated, and the safety and tolerability of the drug will be closely monitored.

Study design schema - BPDCN Expansion Phase



Number of patients (planned):

Overall, it is estimated that approximately 208 patients will be enrolled in this study.

Dose Escalation and AML/ALL/Other Expansion Phase

- Dose Escalation Phase: 65 patients
- AML/ALL/Other Dose Expansion Phase: Approximately 53 patients:
  - Cohort 2: Patients with relapsed AML – 20 patients (closed to enrollment)
  - Cohort 3: Patients with relapsed or refractory ALL – 3 patients (closed to enrollment)
  - Cohort 4: Patients with relapsed or refractory hematologic malignancies not included in the cohorts above (eg, high-risk/very high-risk MDS, myeloproliferative neoplasms [MPN], chronic myelomonocytic leukemia [CMML], BP-CML) – up to 20 patients
  - Cohort 5: Patients with relapsed or refractory (to nonintense therapies) AML at an alternate dose or schedule – 10 patients (closed to enrollment)

BPDCN Expansion Phase

It is estimated that approximately [redacted] BPDCN patients will be enrolled:

- Cohort 1: Patients with relapsed or refractory BPDCN – up to [redacted] patients
- Cohort 6: Patients with frontline de novo BPDCN who have not received prior systemic therapy (up to [redacted] patients) and patients with frontline BPDCN who have a PCHM and have not received prior systemic therapy (approximately [redacted] patients)

Diagnosis and main criteria for inclusion/exclusion:

Inclusion criteria

1. Disease Characteristics:
   a. Confirmation of CD123 positivity by flow cytometry or immunohistochemistry. Patients who received prior CD123-targeting agents will be allowed as long as the blasts still have detectable CD123 expression.
   b. Dose Escalation – Relapsed or refractory AML (excluding acute promyelocytic leukemia) or BPDCN, based on World Health Organization Classification (see Appendix G for definition of clinical relapse).
   c. Dose Expansion:
      - Cohort 1 – Patients with relapsed or refractory BPDCN.
      - Cohort 2 – Patients will have relapsed AML (closed to enrollment).
      - Cohort 3 – Patients will have relapsed or refractory ALL (including any subtypes: B-cell, T-cell, Ph+, and Ph-) (closed to enrollment).
      - Cohort 4 – Patients will have relapsed or refractory "other" hematologic malignancies not included in the cohorts above (eg, high-risk/very high-risk MDS, MPN, CMML, BP-CML). Other CD123+ malignancies may be considered upon discussion with the Sponsor.

        Note: Blast-phase CML is defined as ≥ 30% blasts in blood, marrow, or both and the demonstration of extramedullary infiltrates of leukemic cells.
      - Cohort 5 – Patients will have relapsed or refractory (to nonintense therapies) AML (closed to enrollment)

- Cohort 6 – Patients with frontline de novo BPDCN who have not received prior systemic therapy and patients with frontline BPDCN who have a PCHM and have not received prior systemic therapy

  Note: Patients in Cohort 6 may have received local therapy (radiotherapy, surgical excision, photodynamic therapy). Eligible patients must have a recurrence or progression in the field of local therapy OR disease outside the field of local therapy. Patients identified as having concomitant malignancy while on trial will continue to be identified as de novo BPDCN patients.

2. Patients in the BPDCN Expansion Phase Cohort 1 may have received up to 3 prior lines of systemic therapy (regardless of tagraxofusp-erzs exposure).
3. Age ≥ 18 years of age.
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. If nonambulatory due to a chronic disability, must be Karnofsky performance status > 70.
5. Previous treatment-related toxicities must be resolved to Grade 1 (excluding alopecia).
6. Liver enzymes (aspartate aminotransferase and alanine aminotransferase) ≤ 2.5 × the upper limit of normal (ULN). Exceptions may be made for patients with elevated liver transaminases secondary to the underlying study disease.
7. Total bilirubin ≤ 1.5 × ULN; patients with Gilbert syndrome must have total bilirubin < 3.0 × ULN with direct bilirubin < 1.0 × ULN at the time of enrollment.
8. Estimated glomerular filtration rate of > 30 mL/min/1.73 m^2 or creatinine clearance of > 30 mL/min (Section 4.1).
9. Left ventricular ejection fraction ≥ 45%.
10. Patients with a prior autologous or allogeneic bone marrow transplant are eligible for Cohorts 1 to 5. Patients with an allogeneic transplant must meet the following conditions: the transplant must have been performed more than 120 days before the date of dosing on this study, the patient must not have active ≥ Grade 2 acute graft versus host disease (GvHD), or extensive chronic GvHD of any severity, and must be off all immunosuppression for at least 2 weeks before first dose of IMGN632.
11. Patients or their legally authorized representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), before performance of any study-related procedure not part of normal medical care.
12. Women of childbearing potential (WCBP) patients/partners, defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months) must agree to use acceptable contraceptive methods while on study drug and for at least 7 months after the last dose of study drug (Section 5.3).
13. WCBP must have a negative pregnancy test before the first dose of study drug.
14. Male patients/partners who are able to father children must agree to use an effective method of contraception (eg, condom), even if they have had a successful vasectomy, throughout the study and for at least 4 months after the last dose of IMGN632.
15. Patients with prior malignancy are eligible. Patients with a PCHM are eligible as long as no current therapy is required for the second malignancy (eg, MDS, CMML). Patients with a nonhematologic prior malignancy must be in remission from the prior malignancy. Patients

must have completed all chemotherapy and radiotherapy for prior malignancy at least 6 months before enrollment and all treatment-related toxicities must have resolved to Grade 1 or less.

Note: Patients with prostate cancer or breast cancer on adjuvant hormonal therapy are eligible.

Note: Patients with tumors with a negligible risk for metastasis or death (eg, adequately controlled basal cell carcinoma or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix or breast) are eligible.

16. Patients must not be incarcerated and must be freely willing and able to provide informed consent. Examples of patients unable to freely provide informed consent may include some adults under legal protection measure (eg, under guardianship/curatorship) or unable to express their consent and select adults under psychiatric care. Investigator's discretion should be applied.

Exclusion criteria

1. Patients who, in the judgment of their treating physician, have appropriate standard-of-care therapies will be excluded from Cohorts 1 through 5.
2. Frontline BPDCN patients with central nervous system (CNS) disease will be excluded. A lumbar puncture must be performed during the 28-day Screening period, before drug administration. Relapsed or refractory BPDCN patients with a known history of CNS disease must have been treated locally, have at least 1 lumbar puncture with no evidence of CNS disease, and must be clinically stable before first dose. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is encouraged (see Section 5.2.4.1).
3. Patients with a history of veno-occlusive disease of the liver.
4. Patients with a history of Grade 4 capillary leak syndrome, or noncardiac Grade 4 edema are ineligible, eg, related to tagraxofusp-erzs or other etiology.
5. Corrected QT interval (QT interval corrected using Fridericia's formula) > 480 msec.
6. Myocardial infarction within 6 months before enrollment or has New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities before study entry.
7. Interval from prior cancer therapy:
    a. For frontline BPDCN patients with prior local therapy (eg, radiotherapy), patients must not have received treatment within 14 days before drug administration on this study.
    b. Relapsed or refractory BPDCN patients must not have received any anticancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal, biologic, or any investigational agents within 14 days before drug administration on this study. Patients must have recovered to baseline from all acute toxicity from this prior therapy.
        Note: Patients who have received a checkpoint inhibitor must not have received that therapy within 28 days before drug administration on this study.
8. Clinically relevant active infection including known active hepatitis B or C, human immunodeficiency virus infection, or cytomegalovirus or any other known concurrent infectious disease that, in the judgment of the Investigator, would make a patient inappropriate for enrollment into this study (testing not required).
9. Patients who have undergone a major surgery within 4 weeks (or longer if not fully recovered) before study enrollment.

10. Serious or poorly controlled medical conditions that could be exacerbated by treatment or that would seriously compromise safety assessment or compliance with the protocol, in the judgment of the Investigator.
11. Patients who are pregnant or breast-feeding.
12. Patients who have a history of allergy to IMGN632 or any of its excipients.
13. Patients who received a live vaccine four weeks or fewer prior to enrollment.

Investigational product, dosage, and mode of administration:

Dose Escalation and AML/ALL/Other Expansion Phase: The starting dose for IMGN632 was 0.015 mg/kg, with IMGN632 administered IV on Day 1 of each 21-day cycle (Schedule A).

BPDCN Expansion Phase: The selected dose for IMGN632 is 0.045 mg/kg. IMGN632 will be administered IV on Day 1 of each 21-day cycle (Schedule A).

Duration of treatment and follow-up: Planned treatment consists of 2 cycles (6 weeks). Additional cycles, up to 10 total, may be administered for patients deriving benefit from this regimen, understanding the theoretical concern for increased risk of veno-occlusive disease (sinusoidal obstruction syndrome) with cumulative exposure. On a case-by-case basis after discussion with the Sponsor, continuation of beyond 10 cycles may be considered.

For the purposes of this study, the period of safety observation extends from the time of signed informed consent to the study until the final safety follow-up visit. Patients who discontinue for reasons other than progressive disease (PD) should undergo disease assessments (Section 9.15) every 12 weeks (± 3 weeks) until documentation of PD, the initiation of a subsequent anticancer therapy, or 2 years from the time of discontinuation of study drug, whichever comes first. After documentation of PD or initiation of new anticancer therapy, the patient should be contacted every 12 weeks (± 3 weeks) for survival follow-up, including the subsequent use of anticancer therapy, and reporting of sustained response when appropriate (ie, CR, CRc, etc) for up to 2 years from the time of discontinuation of study drug, or until overall study closure. Patients who discontinue study drug and undergo hematopoietic stem cell transplantation as consolidation will continue to be monitored for 60 days post-transplantation with information related to the transplant and any post-transplant hepatic complications recorded on the reflex transplant electronic case report form (eCRF).

Reference therapy, dosage, and mode of administration:

Not applicable

Criteria for evaluation:

Dose Escalation and AML/ALL/Other Expansion Phase

PK assessments: Blood samples will be collected at predetermined timepoints to assess the PK of IMGN632, total G4723A antibody, and FGN849 (active catabolite).

Safety assessments: Safety will be assessed by reported/elicited adverse events (AEs), laboratory assessments including hematology and serum chemistry, vital signs, physical examination, and left ventricular ejection fraction assessment as indicated. The assessment of treatment-emergent AEs (TEAEs) includes serious AEs (SAEs), AEs leading to study drug discontinuation, and AEs related to the study drug. All AEs occurring from informed consent until 30 days after last study drug administration must be recorded on the AE eCRF regardless of the seriousness, severity, or relationship to study drug.

Antitumor activity: Response assessments will be performed in bone marrow aspirates (BMAs) for differential assessments taken on Cycle 1, Day 21 ± 7 days. Subsequent BMAs should be performed approximately every 1 to 2 cycles as clinically indicated, and at the 30-Day Follow-up visit. Data will also be collected in the event BMAs are performed more frequently. No repeat bone marrow is

necessary if lack of response (CR without minimal residual disease [CR_{MRD}-], CR, CRh, CRi, CRc; BPDCN only], or PR) or PD can be unequivocally diagnosed from peripheral blood tests or if the bone marrow test is considered noncontributory by the Investigator at any timepoint.

BPDCN Expansion Phase

PK assessments: Blood samples will be collected at predetermined timepoints to assess the PK of IMGN632, total G4723A antibody, and FGN849.

Safety assessments: Safety will be assessed by reported/elicited AEs, laboratory assessments including hematology and serum chemistry, vital signs, physical examination, and left ventricular ejection fraction assessment as indicated. All AEs occurring from informed consent until 30 days after last study drug administration must be recorded on the AE eCRF regardless of the seriousness, severity, or relationship to study drug. The assessment of AEs will include TEAEs, SAEs, AEs leading to study drug discontinuation, and AEs related to the study drug.

Efficacy: All 3 areas of potential disease involvement (skin, bone marrow, nodal/visceral) will be assessed to establish any response (Appendix H). Response assessments by BMAs for differential assessments will be made at the end of Cycles 1, 2, 4, and 6, then every 4 cycles thereafter (approximately every 3 months). Nodal/visceral involvement will be assessed by CT/PET after the end of Cycles 2, 4, and 6, and at the end of every 4 cycles thereafter. Following establishment of a response, repeated CT/PET scans will only be required on patients with nodal/visceral disease at baseline, or as indicated clinically. Skin involvement will be assessed by photographs and Modified Severity-Weighted Assessment Tool (mSWAT) at the end of Cycle 1 and 2, and at the end of every 2 cycles thereafter (approximately every 6 weeks). A biopsy of normal appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a CR would exist.

Statistical methods:

All descriptive statistical analyses will be performed using SAS software (version 9.4 or later), unless otherwise noted in the Statistical Analysis Plan (SAP). For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the number of nonmissing values (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a detailed description of patient disposition; patient demographics and baseline characteristics will be summarized. PK data will be presented descriptively and graphically.

The Dose Escalation Phase will follow a standard 3 + 3 cohort design, with each cohort enrolling 3 to 6 patients. Review of safety data and available preliminary PK data will be conducted by the CRC upon completion of each dose escalation cohort, and at the following timepoints: the time at which a DLT is observed in at least 1 patient; and approximately every 2 weeks, to monitor for the occurrence of DLT in all patients. If the DLT rate in escalation is ≥ 33% at any dose level, that dose level will stop enrollment and be considered above the MTD.

During the Dose Expansion Phase of the trial, the CRC will monitor the occurrence of DLTs at least every 4 weeks. If at any time during the Dose Expansion Phase, the DLT rate is greater than 20% across all cohorts at the same dose level, further enrollment to that dose level will be closed, where the DLT occurring during any time of the study treatment period will be included.

[redacted]

[redacted]

The SAP will fully describe the planned analyses for this study and will be written after the final protocol and annotated eCRFs are finalized and before the database lock.

Sample size: During the Dose Escalation Phase, ascending doses of IMGN632 were evaluated to identify the MTD in each schedule using a traditional 3 + 3 design. A total of 65 patients were treated during the Dose Escalation Phase.

After data review and selection of the recommended dose(s) and schedule(s), the Dose Expansion Phase of the study will open. Patients enrolled in this study will be assigned to 1 of the following 6 cohorts. The Dose Expansion Phase of the study will accrue up to 190 patients, which includes up to 20 additional patients if a different dose level or schedule than Dose Expansion Cohort 2 needs to be investigated (Dose Expansion Cohort 5):

Twenty-patient expansion cohorts (Cohorts 2 through 5) were selected to allow measurement of a target CR rate of 60% while having a 90% confidence interval (CI) to exclude a low response rate of 30%. If the observed CR rate is 12/20 (60%), then the 90% CI for CR rate will be 39% to 78%. Assuming the true CR rate is 60%, then the probability of observing at least 9 complete responders (out of 20) is 94%. Cohorts 2, 3, and 5 are now closed to enrollment.

- **Cohort 2:** 20 patients with relapsed AML (closed to enrollment).
- **Cohort 3:** 3 patients with relapsed or refractory ALL (including any subtypes: B-cell, T-cell, Ph+, and Ph-) (closed to enrollment).
- **Cohort 4:** This cohort will enroll up to 20 patients with relapsed or refractory other hematologic malignancies (eg, high-risk/very high-risk MDS, MPN, CMML, BP-CML).
- **Cohort 5:** 10 patients with relapsed or refractory (to nonintense therapies) AML (closed to enrollment).

BPDCN expansion phase

Sample size of target population for formal efficacy analysis:

[redacted]

Primary endpoint

[redacted]

Secondary endpoints

[redacted]

[redacted]

Subgroup analysis

Subgroup analysis for efficacy will be conducted by prior exposure to tagraxofusp-erzs.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AP	accelerated phase
AST	aspartate aminotransferase (SGOT)
AUC	area under the time-concentration curve
BMA	bone marrow aspirate
BP	blastic phase
BPDCN	blastic plasmacytoid dendritic cell neoplasm
CCR	composite complete remission/response
CD123+	positive for expression of the CD123 antigen
C_{max}	maximum plasma drug concentration
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CP	chronic phase
CR	complete remission/response
CRc	clinical complete remission
CRC	cohort review committee
CRF	case report form
CRh	complete remission/response with partial hematologic recovery
CRi	complete remission/response with incomplete recovery
CR_{MRD-}	complete remission/response without minimal residual disease
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOCR	duration of composite complete remission/response
DOR	duration of overall response

Abbreviation or Specialist Term	Explanation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GvHD	graft versus host disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL-3	interleukin-3
IL-3Rα	alpha subunit of the interleukin-3 receptor
IMGN	ImmunoGen, Inc.
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous(ly)
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MPN	myeloproliferative neoplasms
MRD	minimal residual disease
mSWAT	Modified Severity-Weighted Assessment Tool
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PCHM	prior or concomitant hematologic malignancy
PD	progressive disease
Pd	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetics
PO	per os (orally)
PR	partial response
QTc	corrected QT interval

Abbreviation or Specialist Term	Explanation
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WCBP	woman of childbearing potential

SUMMARY OF PROTOCOL AMENDMENTS

Table 1: Summary of Major IMGN632-0801 Protocol Amendments

Amendment No.	Date	Summary of Major Changes
1 (Protocol Version 2.0)	09 October 2017	• The study design was modified to include patients with CD123+ disease based on qualitative criteria (flow cytometry or immunohistochemistry done in a CLIA-certified laboratory) rather than based on demonstration of at least 20% CD123+ blasts. • Definition of dose-limiting toxicity was clarified to exclude treatment-emergent AEs and abnormal laboratory values that are clearly and incontrovertibly related to underlying disease, including the hematologic malignancy, and comorbidities present at enrollment.
2 (Protocol Version 3.0)	13 October 2017	• Updated drug preparation and administration procedures to specify intravenous study drug administration via syringe pump. • To monitor for potential infusion-related reactions, vital signs are recommended to be assessed within 30 minutes prior to dose and approximately every 15 minutes (or as indicated by institutional practice) for at least 1 hour following infusion. For the first infusion of IMGN632, additional assessments will be performed approximately every 30 minutes for at least 4 hours, or longer as clinically indicated. • Monitoring of vital signs following infusion reactions to include monitoring for at least 4 hours following Grade 3 or 4 reactions, with continuing assessment as clinically indicated until full resolution.
3 (Protocol Version 4.0)	29 June 2018	• Added the alternate, fractionated dosing Schedule B (Days 1, 4, and 8 of a 21-day cycle) to explore the therapeutic potential of fractionated dosing in dose escalation. • Added language around infusion-related reactions to support further collection of safety information around the occurrence and nature of infusion-associated symptoms. Signs and symptoms of potential infusion-related reactions were added as an AESI. • Added Expansion Cohort 5 (relapsed AML cohort) to aid in the design of Phase 2 and combination trials. • Allowed patients in dose expansion for AML to have had up to 2 prior therapies rather than just 1 prior therapy. • Allowed refractory BPDCN patients to enroll in the Dose Expansion Phase, in addition to relapsed BPDCN patients. • Added the ability to dose escalate beyond Cohort 6, the highest dose level specified in Amendment 3.0.
4 (Protocol Version 5.0)	15 November 2019	• Broadened the inclusion criteria for BPDCN, AML, and ALL patients. • Increased the clarity of the primary, secondary, and exploratory study objectives and endpoints for the dose escalation cohorts, BPDCN patients, and all patients.

Table 1: Summary of Major IMGN632-0801 Protocol Amendments (Continued)

Amendment No.	Date	Summary of Major Changes
5 (Protocol Version 6.0)	04 February 2021	• Increased the focus of the study on the treatment of BPDCN patients, including frontline patients. • Identified the primary and secondary study objectives and endpoints for the BPDCN dose expansion cohorts.
6 (Protocol Version 7.0)	07 January 2022	• Provided additional premedication the day prior to IMGN632 dosing. • Provided additional exclusion criteria for patients who are pregnant, breastfeeding, or have a history of allergies to IMGN632 or its excipients. • Outlined acceptable highly effective contraception.
7 (Protocol Version 8.0)	21 October 2022	• Expanded Cohort 6 to include patients with frontline de novo BPDCN who have not received prior systemic therapy (up to 20 patients) and patients with frontline BPDCN who have a prior or concomitant hematologic malignancy and have not received prior systemic therapy (approximately 20 patients). Clarified that the de novo population will be used to reject the null hypothesis. • Revised the inclusion criteria to indicate total bilirubin ≤ 1.5 × ULN; patients with Gilbert syndrome, must have total bilirubin < 3.0 × ULN with direct bilirubin < 1.0 × ULN at the time of enrollment. • Revised description of the Dose Escalation and Dose Expansion Cohorts 2, 3, and 5 to indicate that these are closed to enrollment.
8 (Protocol Version 9.0)	30 May 2023	• Revised the safety follow-up period for patients who discontinue IMGN632 and undergo hematopoietic stem cell transplantation as consolidation to include the collection of data related to the transplant and any post-transplant hepatic complications for 60 days post-transplantation.

Table 1: Summary of Major IMGN632-0801 Protocol Amendments (Continued)

Amendment No.	Date	Summary of Major Changes
9 (Protocol Version 10.0)	20 November 2024	• Updated Sponsor and Sponsor contact information and EU CT number. • Updated inclusion criterion #11 to comply with company EU CTR standards. • Added inclusion criterion #16 that patients must not be incarcerated and must be freely willing and able to provide informed consent to comply with company EU CTR standards. • Added additional EU CTR-compliant language to adhere to EU regulations No. 536/2014 Annex A to the following sections: o Added section for Appropriateness of Measures to comply with company EU CTR standards. o Updated section on Study Drug Storage to contain language that complies with company EU CTR standards. o Updated section on Sponsor's Responsibility to Inform to contain language that complies with company EU CTR standards. o Added text to section on Quality Control and Assurance to comply with company EU CTR standards. o Added text to section on Investigators and Study Administrative Structure to comply with company EU CTR standards. o Added text to section on Ethical Conduct of the Study to comply with company EU CTR standards. o Added text to section on Patient Confidentiality to comply with company EU CTR standards. o Added section for Start and Completion of the Study to comply with company EU CTR standards. o Added section For EU CTR Submissions Publication Policy to comply with company EU CTR standards.

AE = adverse event; AESI = adverse event of special interest; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CLIA = Clinical Laboratory Improvement Amendments; CT = clinical trial; CTR = Clinical Trials Regulation; EU = European Union; ULN = upper limit of normal.

1. INTRODUCTION

CD123 is also known as the alpha subunit of the interleukin-3 receptor (IL-3Rα). Interleukin-3 (IL-3) is produced by activated T-lymphocytes. IL-3 together with other growth factors stimulates the development and mediates the survival of a wide range of hematopoietic cells in bone marrow (Testa 2014). CD123 levels on normal hematopoietic stem cells are very low, but early common myeloid progenitors express higher CD123 levels (Testa 2014, Jordan 2000). Medium to high expression of CD123 on normal tissues is limited to rare populations of white blood cells, such as plasmacytoid dendritic cells and basophils (Jordan 2000, Testa 2014).

Recent studies indicate that CD123 may contribute to the proliferative advantage of leukemic cells and is overexpressed in multiple hematologic malignancies of both myeloid and lymphoid origins. The highest CD123 levels were reported for patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) (Garnache-Ottou 2009, Kharfan-Dabaja 2013, Julia 2014). Greater than 95% of acute myeloid leukemia (AML) cases are CD123+ (Jordan 2000, Muñoz 2001, De Smet 2012, Ehninger 2014) and similar prevalence of CD123 expression were reported for B-cell acute lymphoblastic leukemia (B-ALL), hairy cell leukemia, chronic myeloid leukemia in the blastic phase (BP-CML), and the high-risk myelodysplastic syndrome (MDS) (Florian 2006, De Smet 2012, Coustan-Smith 2011, Venkataraman 2011, Nievergall 2014). Several reports indicate that 60% of Hodgkin lymphoma, 60% of systemic mastocytosis, and 30% of mantle cell lymphoma patients overexpress the receptor (Fromm 2011, Venkataraman 2011, Pardanani 2015, Pardanani 2016). Moreover, CD123 levels on leukemic stem cells are at least as high as those on leukemic progenitors and mature leukemic cells in AML, CML, and MDS, consistent with the role of CD123 in proliferation and survival of leukemic progenitors and leukemic stem cells. Therefore, CD123-targeted therapies have the potential to reduce leukemia cell burden as well as eliminate leukemic stem cells, leading to durable responses and potential cures.

1.1. IMGN632 and Populations to Be Studied

IMGN632 is an antibody-drug conjugate consisting of an anti-CD123 monoclonal immunoglobulin G1 (IgG1) antibody (G4723A) attached via a succinimide linkage to the DGN549-C linker-payload, which consists of the FGN849 payload (active moiety) and peptide linker change. IMGN632 binds to CD123+ cells and, upon intracellular processing, releases a highly potent and cell membrane-permeable payload, FGN849. FGN849 is a member of the novel indolinobenzodiazepine pseudodimer (IGN) class of cytotoxic molecules that bind to the minor groove of DNA, leading to DNA alkylation, apoptosis, and cell death.

1.1.1. Targeted Indications

1.1.1.1. Acute Myeloid Leukemia

AML is the most common type of acute leukemia among adults in the United States (US) and European Union (EU). In the US, an estimated 19,950 people will be diagnosed with AML in 2016, and 10,430 patients will die of the disease (Siegel 2016). Similarly, approximately 19,000 people will be diagnosed in the EU, with an incidence of 3.7 per 100,000 (Visser 2012). The median age of diagnosis is 66 years.

Over the past decade, refinements in the diagnosis of subtypes of AML and advances in therapeutic approaches have slightly improved the outcome for patients with AML. Frontline chemotherapy in AML is reported to induce complete remission/response (CR) in 70% to 80% of patients who are 60 years of age or younger and in approximately 50% of older patients (Döhner 2017). "Fit" patients are judged to be able to tolerate intensive treatment, are often younger (< 60 years), and typically receive 1 to 2 cycles of induction with "7 + 3," a combination of cytarabine and anthracycline, typically daunorubicin. Following this, these fit patients may receive high dose cytarabine for 1 or more cycles and may receive a stem cell transplant. Standard induction and post-induction therapies result in a 5-year survival rate of approximately 28% (SEER 2018). "Unfit" patients, often older, typically receive azacitidine, a hypomethylating agent, with or without venetoclax. Approximately 30% to 60% of these patients will obtain a CR. However, most AML patients are refractory to treatment or will relapse, and AML salvage regimens offer poor outcomes with significant toxicity. Thus, novel therapies with limited toxicity in this relapsed population are needed, and such patients represent an appropriate population for an initial IMGN632 therapeutic trial.

Despite these improvements, the majority of AML patients will eventually relapse. The 5-year overall survival (OS) rate is only about 25% (SEER 2018). Additionally, primary refractory AML and early relapse remain among the most challenging scenarios in the management of AML. Primary refractory or resistant disease as defined by not achieving CR (ie, a remaining blast count of ≥ 5% after 1 to 2 cycles of intense induction therapy) occurs in 10% to 40% of the patient population (Cheson 2003, Thol 2015).

1.1.1.2. Blastic Plasmacytoid Dendritic Cell Neoplasm

BPDCN is a rare, aggressive hematologic malignancy derived from myeloid dendritic cell precursors, which often manifests with skin lesions in addition to lymph node, blood, and bone marrow involvement. Although the exact incidence of BPDCN is unknown, it represents approximately 0.44% of all hematologic malignancies, less than 1% of acute leukemias, and 0.7% of cutaneous lymphoma cases (Pagano 2013, Riaz 2014). It occurs most commonly in elderly males and is most often diagnosed in Stage IV. It manifests initially with cutaneous lesions and, commonly, mild to moderate peripheral cytopenias, eventually developing to fulminant leukemia. Advanced age and clinical stage are poor prognostic indicators.

Intense chemotherapy and tagraxofusp-erzs (ELZONRIS®, approved in the US in 2019) are standard of care in frontline BPDCN in Europe and the US. Tagraxofusp-erzs, which targets IL-3Rα (CD123), was shown to induce responses in the majority of patients with BPDCN and provides evidence that targeting CD123 can be an effective strategy in BPDCN patients (Pemmaraju, Lane 2019). In treatment-naïve BPDCN patients, tagraxofusp-erzs is associated with a CR/complete clinical remission/response (CRc) rate of 54% (7/13 patients), and in relapsed BPDCN, a CR/CRc rate of 13% (2/15 patients). Tagraxofusp-erzs is associated with capillary leak syndrome, hypersensitivity reactions, and hepatotoxicity (US Food and Drug Administration [FDA] package insert). Remission rates of 41% to 94% are observed in frontline disease (Aoki 2015), and many remissions are consolidated with stem cell transplant. The majority of BPDCN patients will relapse with no effective salvage treatment options; therefore, BPDCN represents a disease with a high unmet need.

Although the majority of patients have de novo BPDCN, it has been recognized that at least 25% of BPDCN patients have a prior or concomitant hematologic malignancy (PCHM) (eg, chronic myelomonocytic leukemia [CMML], MDS, myeloproliferative neoplasms [MPN], AML) (Pemmaraju, Kantarjian 2019). Both patients with de novo and PCHM BPDCN will be eligible to enroll in this study.

1.1.1.3. Acute Lymphocytic/Lymphoblastic Leukemia (B-Cell Origin)

ALL is a rare, aggressive hematologic malignancy derived from lymphoid precursors, which often manifests with lymph node, blood, and bone marrow involvement. ALL is a heterogeneous group of disorders, and approximately 80% is of a B cell phenotype (Moorman 2010). It is estimated that approximately 6590 new cases of ALL will be diagnosed in 2016 in the US, and approximately 1430 patients will die of their disease (Siegel 2016). Similarly, approximately 6500 people will be diagnosed in the EU each year (Hoelzer 2016). B-cell ALL and some T-cell ALL blasts express CD123 at levels similar to AML blasts and thus represent an appropriate patient population for anti-CD123-targeted therapy.

Although initial remission rates are high, long-term survival rates are approximately 80% for children, 35% to 40% in patients less than 60 years of age, and less than 10% for older patients (Goldstone 2008). Patients with relapsed ALL have several chemotherapeutic options, as well as immunotherapy with United States FDA-approved anti-CD19 bispecific blinatumomab. However, long-term survival has been < 25% for these patients (Frey 2015), and therefore the relapsed/refractory population represents an appropriate population for an initial IMGN632 therapeutic trial.

1.1.1.4. Other CD123+ Hematologic Malignancies

High-Risk MDS

MDS is a heterogeneous group of myeloid disorders defined by a common set of features, of which the most prominent is morphologic bone marrow and peripheral blood dysplasia associated with inefficient hematopoiesis, the development of peripheral cytopenias, and a risk of transformation to AML (Mufti 2008). The incidence of MDS is approximately 3 to 4 cases per 100,000 individuals annually and 20 cases per 100,000 per year in patients > 70 years of age (Rollison 2008). Patients with intermediate-2 and high-risk MDS are at high risk of progressing to AML and have a survival rate of 0.4 to 1.2 years. Allogeneic bone marrow transplant is the only available treatment with curable potential; however, this option is not available to most MDS patients due to advanced age and comorbid conditions associated with an elderly population (Mufti 2008).

BP-CML

It is estimated that 8220 new cases of CML will be diagnosed and 1070 patients will die in the United States in 2016 (Siegel 2016). Chronic myeloid leukemia is a myeloproliferative disorder that can occur with a bi- or triphasic course. It is characterized by a chronic phase (CP), an accelerated phase (AP), and a BP (Calabretta 2004). Patients with CP-CML live many years due in part to recent scientific advances in the area of targeted treatments like imatinib and other tyrosine kinase inhibitors (American Cancer Society 2016). Treatment of newly diagnosed patients with CP-CML with tyrosine kinase inhibitors results in near-normal life expectancy

(Pearson 2016). Seventy-five percent to 80% of patients go through an AP before BP. The definitions for AP- and BP-CML are not uniform. In this protocol, BP-CML is defined as ≥ 30% blasts in blood, marrow, or both, and the demonstration of extramedullary infiltrates of leukemic cells (NCCN 2016). Data showed that patients with 20% to 29% blasts have an outcome similar to patients with AP criteria (less than 29% blasts but more than 15% blasts in blood or bone marrow), having a median survival approximately 12 months longer than those with blasts ≥ 30% (Coiffier 2012). In general, AP-CML lasts 9 to 12 months, and BP-CML or blast crisis lasts only a few months and is the terminal phase of the disease course. With the exception of patients who can undergo allogeneic bone marrow transplantation during the CP, transition to BP and ultimately death is the inevitable outcome (Weisdorf 2002).

1.2. Nonclinical Studies of IMGN632

Results of nonclinical in vitro and in vivo pharmacology studies demonstrate the following:

- CD123 expression on normal hematopoietic stem cells is very low, but early common myeloid progenitors express higher CD123 levels, and medium to high expression of CD123 on normal tissues is limited to rare populations of white blood cells, such as plasmacytoid dendritic cells and basophils. In contrast, strong expression was observed in patient-derived AML and ALL samples.
- In vitro studies demonstrated that IMGN632 binds cell surface CD123 with high apparent affinity (Kd of approximately 0.1 nM).
- Treatment of CD123+ AML cells with IMGN632 leads to DNA damage, arrest in S phase of the cell cycle, and apoptosis-mediated cell death.
- IMGN632 demonstrated strong CD123-dependent cytotoxicity in vitro in AML patient-derived cells and in AML cell lines with known poor prognostic markers, including the internal tandem duplication in the Fms-like tyrosine kinase-3 gene (FLT3-ITD), ecotropic viral integration site 1 protein overexpression, and mutations in the p53 gene. In addition, IMGN632 was highly cytotoxic in vitro in ALL cell lines with poor prognostic markers and CD123 dependent. The potent and CD123-dependent activity of IMGN632 has been demonstrated in vitro using the [redacted]
- Studies in xenograft mouse models of EOL-1 and MV4-11 (an FLT3-ITD model) AML cells demonstrated high CD123-dependent activity. [redacted]
- IMGN632 did not cause a significant release of cytokines in vitro by normal human peripheral blood cells, indicating a low potential for cytokine release syndrome or immunoproliferative reactions in patients.

Additional details on nonclinical pharmacology studies are provided in the current version of the IMGN632 Investigator's Brochure.

1.2.1. Pharmacokinetics

Nonclinical studies were conducted to evaluate the pharmacokinetics (PK) of IMGN632, total G4723A antibody (total antibody), FGN849 (active catabolite), and antidrug antibodies (ADA) in rodents and nonhuman primates. These studies are detailed in the IMGN632 Investigator's Brochure.

1.2.2. Toxicology

IMGN632 does not cross-react with CD123 in standard toxicology animal species (mouse, rat, or cynomolgus monkey). The lack of cross-reactivity in a toxicologically relevant model makes assessment of targeted toxicity unfeasible in vivo. However, given the highly restricted nature of CD123 expression, evaluation of the nontargeted toxicity of IMGN632 in a non-cross-reactive species will be informative with regard to the potential off-target toxicities that may be observed in patients.

The nontargeted toxicity and toxicokinetic profile of IMGN632 when administered as a single intravenous (IV) (10-minute) infusion was evaluated in a Good Laboratory Practice (GLP) toxicology study in male and female cynomolgus monkeys. There were no test article-related effects on body weights, coagulation, urinalysis, ophthalmic examinations, heart rate, electrocardiogram (ECG) intervals, ECG waveform morphology, blood pressure, or respiration rate measurements. The primary test article–related findings included dermal observations of desquamation and darkened/reddened areas on various body surfaces and/or at the infusion site in all treatment groups, edema and hemorrhage in the skin in all treatment group females and in males in the 0.6 mg/kg group, and lower reticulocyte counts in all treatment groups. The majority of findings resolved by the end of the 28-day recovery period with the exception of dark red discoloration of the infusion site noted in the 0.1 and 0.3 mg/kg/dose group females, scabbing in the 0.6 mg/kg/dose group females, and edema and hemorrhage in the skin in all treatment group females.

The highest non-severely toxic dose (HNSTD) was considered to be between 0.3 and 0.6 mg/kg, and the no observed adverse effect level (NOAEL) was considered to be 0.3 mg/kg.

In addition, IMGN632 and the payload FGN849 were evaluated for toxicity in non-GLP single-dose IV studies in cynomolgus monkeys, Sprague Dawley rats, and/or CD-1 mice, FGN849 was evaluated in a non-GLP repeat-dose study in rats, and IMGN632 was evaluated in a GLP repeat-dose IV infusion study in cynomolgus monkeys. Briefly, in nonclinical toxicology studies in multiple species, the test article–related effects of IMGN632 and FGN849 included body weight loss and decreased food consumption, hematopoietic suppression (bone marrow and lymphoid tissue depletion), increases in liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transferase, sorbitol dehydrogenase [measured in rats only], and total bilirubin), single-cell gastrointestinal tract necrosis, skin discoloration, and microscopic edema. Generally, trends of recovery to baseline were noted. No risks were identified for the cardiovascular, respiratory, or central nervous systems. There were no IMGN632-related ophthalmic findings. The details of the nonclinical toxicology results are provided in the current version of the IMGN632 Investigator Brochure.

1.3. Rationale for Dose Selection

1.3.1. Starting Dose for Escalation

The selection of the maximum recommended starting dose for this clinical trial was performed according to International Conference on Harmonisation (ICH) S9 guidance and is consistent with historical starting dose calculations for antibody-drug conjugates (Saber 2015). The HNSTD could not be defined in the GLP cynomolgus monkey study. Therefore, the NOAEL of 0.3 mg/kg was used to determine the maximum recommended starting dose. Using body weight scaling, the chosen clinical starting dose of IMGN632 is 0.015 mg/kg, which is 1/6 the NOAEL observed in the cynomolgus monkey (cyno) toxicology study. Specifically, the value represents 1/6 of 0.3 mg/kg, scaled to mg/m^2, and then calculated as a flat dose for a human with body surface area = 1.74 m^2 and weight = 70 kg:

$$1/6 \times 0.3 \text{ mg/kg (cyno NOAEL)} \times 12 \text{ (cyno conversion factor to mg/m}^2\text{)} = 0.6 \text{ mg/m}^2$$

$$0.6 \text{ mg/m}^2 \times 1.74 \text{ m}^2 \times 1/70 \text{ kg} = 0.0149 \text{ mg/kg} \approx 0.015 \text{ mg/kg}$$

1.3.2. Dose Expansion

Based on nonclinical pharmacology, clinical safety, PK, and pharmacodynamic (Pd) assessments during the Dose Escalation Phase of the study, a dose of 0.045 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohorts 1, 2, 3, 4, and 6, and a dose of 0.09 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohort 5. Schedule B is no longer being explored.

1.4. Benefit-Risk Considerations

This is the benefit-risk clinical trial with IMGN632 and, therefore, the benefit-risk analysis considerations are based on nonclinical and early clinical data.

Nonclinical toxicology studies reveal that the potential risks of treatment with IMGN632 may include gastrointestinal, hematologic, skin, and peripheral vascular (edema) toxicities. Single-dose toxicity studies indicated a trend or recovery to baseline at necropsy.

Additional adverse events (AEs) not previously observed in animals may also occur in humans.

Some patients have experienced Grade 1 to Grade 3 infusion-associated symptoms (eg, tachycardia, chills, and fever). The majority of events occurred within 1 to 3 hours of receiving IMGN632 and resolved within 24 hours without intervention. Therefore, infusion-related reactions will be considered adverse events of special interest (AESI) as outlined in Section 6.5.3). Please refer to the Investigator's Brochure for further safety information.

Patients in this clinical study will be monitored closely for the development of AEs that may result from study drug administration.

Based upon the nonclinical data, CD123-targeted therapies have a potential to both reduce leukemia cell burden as well as eliminate leukemic stem cells. Since the primary purpose of this clinical study is to provide information on the safety and assessment of activity/efficacy of the investigational therapy in selected disease states, it cannot be presumed that patients will derive benefit from study participation.

Patients with relapsed hematologic malignancies, particularly those with AML, ALL, and BPDCN, have limited effective therapeutic options, and survival after relapse is < 25%, demonstrating a very high unmet need. This study is not meant to replace established therapy, nor should it be offered in lieu of appropriate standard-of-care therapies.

Based upon the available data, the benefit-risk ratio for the use of IMGN632 in this population is favorable and supports investigation in humans.

1.5. Clinical Hypothesis

[redacted] Analysis of the safety, tolerability, PK, and antileukemia activity data obtained in this study will help guide future development of IMGN632.

The proposed Phase 1/2 study is an open-label, benefit-risk study of IMGN632 monotherapy in patients with AML, BPDCN, ALL, and other CD123+ hematologic malignancies. IMGN632 will be administered in Schedule A on Day 1 of each 21-day cycle and in Schedule B at an alternate regimen approved by the cohort review committee (CRC) (eg, Days 1, 4, and 8) based on ongoing review of safety, PK/Pd, and antileukemia activity data. The Dose Escalation Phase will follow a 3 + 3 cohort design, with each cohort enrolling 3 to 6 patients, and will proceed following the modified Fibonacci schema in Table 2 until the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for a given schedule are defined. In the Dose Escalation Phase of the study, the MTD for a given schedule will be determined from the assessment of dose-limiting toxicities (DLTs) during the first dosing cycle. A CRC will convene after each cohort and at other prespecified periods to review the available safety, PK, and Pd data, along with leukemic activity data, before escalating to the next dose level. The RP2D(s) and recommended schedule(s) to be evaluated in the dose expansion portion of the study will be determined based on available safety, PK, and Pd data. The selected RP2D for a given disease or patient population will be used during the Dose Expansion Phase of the study. The expansion cohorts are designed to detect antileukemia activity in frontline, relapsed, or refractory BPDCN, relapsed or refractory AML, relapsed or refractory ALL, and other relapsed or refractory CD123+ hematologic malignancies.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Dose Escalation and AML/ALL/Other Expansion Phase

2.1.1. Primary Objective and Endpoints

- To determine the maximum tolerability of IMGN632 on the selected dosing schedule(s)
  - MTD and RP2D

2.1.2. Secondary Objectives and Endpoints

- To characterize the safety profile and tolerability of IMGN632 when given as a single agent across dose levels and schedules
  - Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and DLTs
- To characterize the PK of IMGN632, total antibody, and FGN849 (active catabolite)
  - PK parameters, including but not limited to observed maximum plasma concentration (C_{max}) and area under the concentration versus time curve (AUC)
- To evaluate the potential immunogenicity of IMGN632
  - ADA
- To assess the antileukemia activity in AML, ALL, and other patients (tumor-specific expansion cohorts):
  - Overall response rate (ORR) (CR without minimal residual disease [CR_{MRD-}] + CR + complete remission/response with partial hematologic recovery [CRh] + complete remission/response with incomplete recovery [CRi] + morphologic leukemia-free state [MLFS] + partial response [PR]), complete remission rate (CR_{MRD-}, CR, CRh), composite complete remission/response (CCR) rate (CR_{MRD-}, CR, CRh, CRi), and time to event outcomes (duration of overall response [DOR], event-free survival, relapse-free survival, OS)

2.1.3. Exploratory Objectives and Endpoints

- To characterize the Pd profile of IMGN632, by assessing target saturation by IMGN632 and persistence of saturation, during the dose escalation portion of the study
  - CD123 receptor occupancy in blood and bone marrow by flow cytometry

[redacted]

[redacted]

2.2. BPDCN Expansion Phase (Cohorts 1 and 6)

2.2.1. Primary Objective and Endpoints

- To assess the rate of CCR in frontline de novo BPDCN patients in Cohort 6
  - CR+clinical CR (CRc)

2.2.2. Secondary Objectives and Endpoints

- To assess the rate of CCR: CR+CRc
  - CR+CRc
- To assess the duration of CCR (DOCR) for patients with CR or CRc in frontline de novo BPDCN patients in Cohort 6: CR+CRc
- To assess the DOCR for relapsed/refractory and other frontline patients with CR or CRc in Cohorts 1 and 6
- To characterize the safety profile and tolerability of IMGN632 when given as a single agent at the RP2D level
- To assess the rate of CR+CRc+CRh
- To assess the duration of CR+CRc+CRh
- To assess ORR: CR+CRc+CRh+CRi+PR
- To assess DOR
- To assess OS
- To assess the percent of BPDCN patients able to bridge to stem cell transplant in the frontline and relapsed/refractory populations separately
- To characterize the PK of IMGN632, total antibody, and FGN849 (the active catabolite)
- To evaluate the potential immunogenicity of IMGN632
  - ADA
- To assess transfusion independence
  - Conversion rate to independence of red blood cell and platelet transfusion relative to baseline

[redacted]

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is an open-label, multicenter, Phase 1/2 study to determine the MTD, RP2D if different, and recommended dosing schedule for IMGN632 monotherapy and to assess the safety, tolerability, PK, immunogenicity, and antileukemia activity of IMGN632 when administered to patients with CD123+ hematologic malignancies.

This clinical study will be conducted in compliance with the protocol, ICH E6 Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

This study comprises a Dose Escalation Phase followed by a Dose Expansion Phase. The Dose Escalation Phase will establish the MTD(s) for IMGN632 when given on different schedules and will explore the safety profile and antileukemia activity at selected RP2D(s) and recommended schedule(s). The Dose Expansion Phase will include treatment with IMGN632 at different dose levels and schedules in AML/ALL/Other (Section 3.1.1) and BPCDN (Section 3.1.2) populations (Figure 1).

3.1.1. Dose Escalation and AML/ALL/Other Expansion Phase

For dose escalation, eligible patients were ≥ 18 years of age and had relapsed/refractory CD123+ AML or BPDCN. The Dose Escalation Phase followed a standard 3 + 3 cohort design. Two dosing schedules were evaluated in this portion of the study:

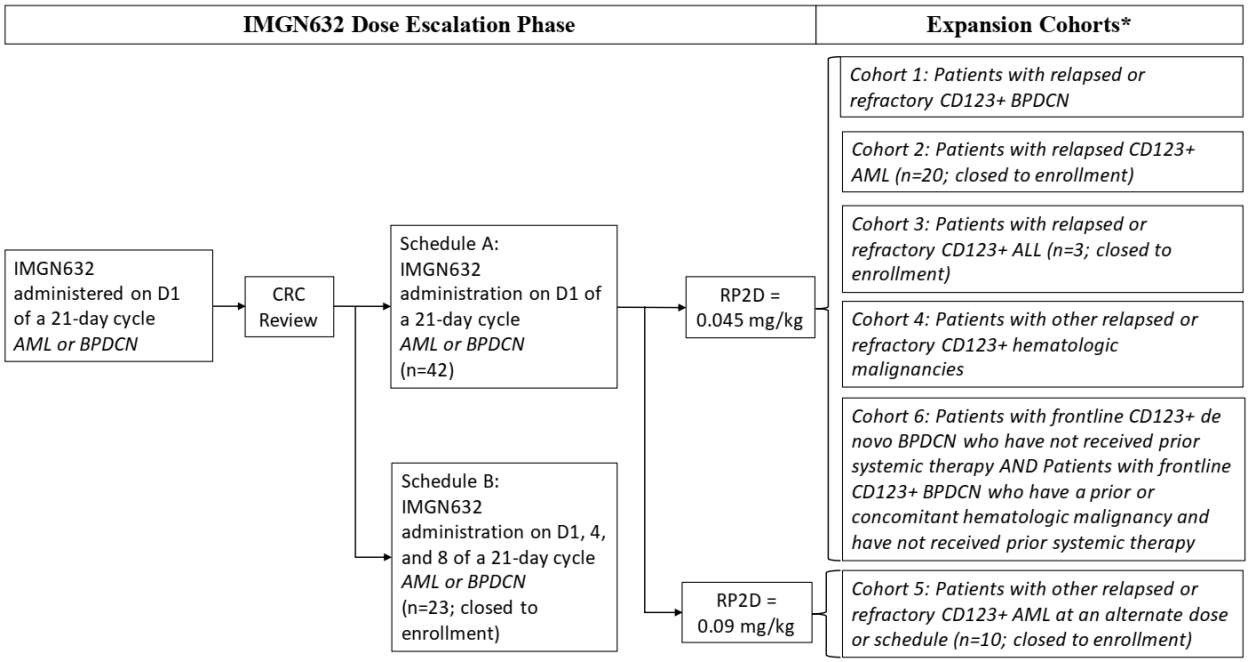
- Schedule A: IMGN632 administered on Day 1 of a 21-day cycle
  - The starting dose for IMGN632 was 0.015 mg/kg (see Section 1.3). The dose escalation regimen ranged from 3-fold with the first dose escalation to 1.5-fold with the last dose escalation. The rationale for the 3-fold increase in dose between Cohort 1 and Cohort 2 was based upon the use of a non-cross-reactive toxicology species to determine the NOAEL and the increased clearance of IMGN632 predicted in patients based on interspecies scaling.
- Schedule B: IMGN632 administered on an alternate dosing schedule (Days 1, 4, and 8 of a 21-day cycle)
  - The maximum starting dose for Schedule B was determined by the CRC based on available safety, Pd, and PK data from the last dose cleared on Schedule A. IMGN632 was administered in equal fractions across Days 1, 4, and 8 of a 21-day cycle (eg, 1/3 of the total dose administered on Schedule A on each of Days 1, 4, and 8).

Study enrollment opened with IMGN632 being administered on Schedule A (Table 2).

PK and Pd parameters were evaluated, and the safety and tolerability of the drug were closely monitored. At the end of the 21-day cycle, study patients were eligible for further treatment at the same dose level of their respective dose escalation cohort in the absence of progressive disease (PD), treatment intolerance, or withdrawal of consent.

Patients were enrolled into cohorts using a standard 3 + 3 design. A total of 65 patients were enrolled during the Dose Escalation Phase, 42 patients under Schedule A and 23 patients under Schedule B. Based on nonclinical pharmacology, clinical safety, PK, and Pd assessments during the Dose Escalation Phase of the study, a dose of 0.045 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohorts 1, 2, 3, 4, and 6, and dose of 0.09 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohort 5. Schedule B is no longer being explored (Figure 1).

Figure 1: Study Design Schema



*Dose expansion cohorts were planned in patient populations as described by Cohorts 1 through 6. Cohort 1 will enroll up to [redacted] relapsed or refractory BPDCN patients. Up to [redacted] frontline CD123+ BPDCN patients who have not received prior systemic therapy are planned to be enrolled in Cohort 6 (up to [redacted] patients with frontline de novo BPDCN and up to [redacted] patients with BPDCN who have a prior or concomitant hematologic malignancy). Enrollment in Cohort 4 is planned for up to [redacted] patients per cohort. Enrollment in Cohorts 2, 3, and 5 is closed.

Table 2: Planned Dose Escalation Cohorts – Schedule A

Dose Escalation Cohorts	IMGN632 (mg/kg/dose)	Fold Dose Increase Over Prior Dose Level
1	0.015	--
2	0.045	3
3	0.09	2
4	0.18	2
5	0.3	1.67
6	0.45	1.5
7	0.67	1.5
8	1.0	1.5

The monitoring of DLTs across all cohorts at the same dose level will use a frequentist approach using a maximum probability of DLT of 20% as stopping rule (Section 3.3.4).

Planned treatment consists of 2 cycles (6 weeks). Additional cycles, up to 10 total, may be administered for patients deriving benefit from this regimen, understanding the theoretical concern for increased risk of veno-occlusive disease (sinusoidal obstruction syndrome) with cumulative exposure. On a case-by-case basis after discussion with the Sponsor, continuation beyond 10 cycles may be considered.

3.1.1.1. Cohort Review Committee

The CRC comprises a Sponsor Medical Monitor and Pharmacovigilance Representative and Investigators from participating sites. A CRC charter will outline the responsibilities of this committee. Once the last patient in a given cohort has completed the first cycle of treatment (defined as 21 days), a CRC meeting will be convened to review all available safety data and decide whether to

- Continue escalation to the next higher or intermediate dose level
- Add patients to a cohort based on the 3 + 3 design
- Pause dose escalation for a specific schedule
- Open Schedule B, including selection of the starting dose and schedule
- Modify the dosing schedule on Schedule B (ie, eliminate Day 4)
- Further explore the current and/or lower dose levels in a given schedule

In addition to end-of-cohort meetings, the CRC will convene to review data at the following timepoints: the time at which a DLT is observed in at least 1 patient and approximately every 2 weeks thereafter to monitor for the occurrence of the DLT in all patients. During the Dose Expansion Phase of the study, the CRC will monitor the occurrence of DLTs at least every 4 weeks.

3.1.1.2. Dose Expansion Cohorts

Based on nonclinical pharmacology, clinical safety, PK, and Pd assessments during the Dose Escalation Phase of the study, a dose of 0.045 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohorts 1, 2, 3, 4, and 6, and dose of 0.09 mg/kg administered on Day 1 of a 21-day cycle (Schedule A) was selected for Cohort 5. Schedule B is no longer being explored. The 2 cohorts in AML (Cohort 2 and Cohort 5) explored differences in efficacy and safety between 2 different doses on 2 different schedules to aid in the design of Phase 2 and combination studies. The other expansion cohorts will assess signs of activity in patients with BPDCN, ALL, and other CD123+ hematologic malignancies. This approach will enable future studies in these patient populations.

- Cohort 2: Patients with relapsed AML – 20 patients (closed to enrollment)
- Cohort 3: Patients with relapsed or refractory ALL – 3 patients (closed to enrollment)
- Cohort 4: Patients with relapsed or refractory hematologic malignancies not included in the cohorts above (eg, high-risk/very high-risk MDS, MPN, CMML, BP-CML) – up to 20 patients
- Cohort 5: Patients with relapsed or refractory (to nonintense therapies) AML at an alternate dose or schedule – 10 patients (closed to enrollment)

3.1.2. BPDCN Expansion Phase

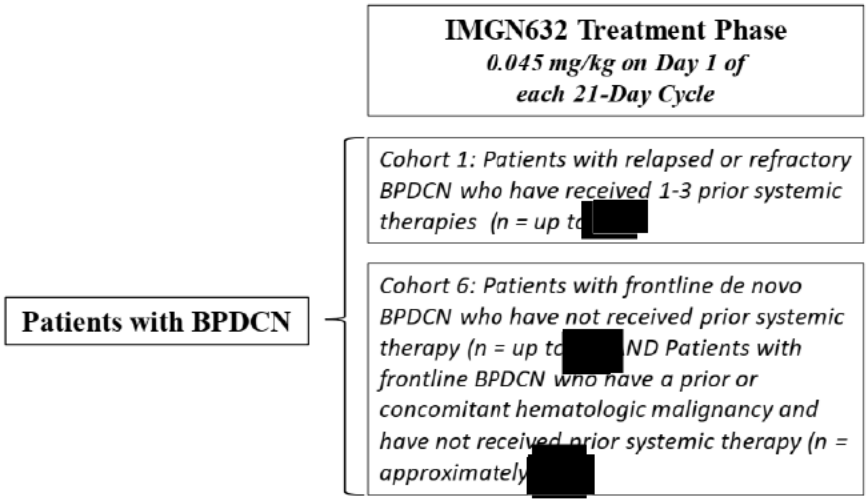
Patients with BPDCN will be enrolled into one of the following cohorts:

- Cohort 1: Patients with relapsed or refractory BPDCN who have received 1 to 3 prior systemic therapies (including tagraxofusp-erzs and/or any other therapy deemed appropriate for the treatment of BPDCN) – up to [redacted] patients
- Cohort 6: Patients with frontline de novo BPDCN who have not received prior systemic therapy (up to [redacted] patients) and patients with frontline BPDCN who have a PCHM and have not received prior systemic therapy (approximately [redacted] patients)

All patients will receive the RP2D of 0.045 mg/kg IMGN632 by IV infusion on Day 1 of a 21-day cycle. All 3 areas of potential disease involvement (skin, bone marrow, nodal/visceral) will be assessed to establish a response; subsequently repeated computed tomography/positron emission tomography (CT/PET) scans will only be performed on patients with nodal/visceral disease at baseline, or as indicated clinically. Bone marrow and skin assessments will continue per schedule for all patients (Appendix C).

PK will be evaluated, and the safety and tolerability of the drug will be closely monitored.

Figure 2: BPDCN Expansion Phase Design Schema



3.1.3. Population Evaluable for Dose-Limiting Toxicities

Evaluable patients will include all patients who received at least 1 dose during the first cycle of therapy. A qualifying AE occurring after dosing of IMGN632 during Cycle 1 will be considered a DLT.

3.1.4. Definition of Dose-Limiting Toxicity

DLTs will be defined as all TEAEs or abnormal laboratory values that meet the DLT criteria outlined below, including those TEAEs and abnormal laboratory values that result in a failure to meet the criteria for retreatment, unless clearly and incontrovertibly related to underlying disease, including the hematologic malignancy, and comorbidities present at enrollment.

Only DLTs that occur during the first cycle will be required for decisions regarding dose escalation. Clinically significant toxicities or adverse events that meet the definition of dose-limiting that occur after Cycle 1 may be considered in subsequent escalation decisions when appropriate and in determination of both the MTD (pausing dose escalation) and RP2D.

If at any time during the study a patient experiences a potential DLT as outlined in Table 3, enrollment will be paused within that cohort and may also be paused in ongoing cohorts at the discretion of the Sponsor until CRC review. For patients with a DLT in Cycle 1, further IMGN632 dosing must be delayed and the toxicity in question must be followed until resolution to ≤ Grade 2 or return to baseline.

If a patient experiences a hematologic DLT or aplasia (ie, bone marrow cellularity < 5%) within Cycle 1 requiring greater than 21 days of observation as defined in Table 3, the DLT observation period will be extended to Day 42, study drug will be held for that patient, and dose escalation and enrollment into the cohort will pause. Patients in the affected cohort or at lower dose levels may continue treatment at the same dose level until the end of the extended DLT observation period. If the hematologic DLT or aplasia has resolved, then escalation may continue at the next planned dose level, and dosing for that patient may resume. If the hematologic DLT or aplasia

has not resolved, the cohort may be expanded to allow for additional observation at that dose level following the defined escalation/MTD dose determination procedures (see Section 3.3.1).

Table 3: Dose-Limiting Toxicity

Toxicity	Criteria
Hematology	Failure of recovery to an absolute neutrophil count of ≥ 0.5 × 10^9/L and/or platelet count of ≥ 25 × 10^9/L, when bone marrow otherwise indicates remission, by 42 days after the first day of study drug. Aplasia (ie, bone marrow cellularity < 5%) that does not recover within 42 days after the first day of study drug. Lack of count recovery if active marrow disease is demonstrated is not considered a dose-limiting toxicity (DLT).
Gastrointestinal	≥ Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 vomiting or nausea despite the use of optimal antiemetic treatments ≥ CTCAE Grade 3 diarrhea despite the use of optimal antidiarrheal treatments
Renal	Serum creatinine ≥ 3.0 × upper limit of normal (ULN) (except for isolated elevations – see below)
Hepatic	Bilirubin, alanine aminotransferase, or aspartate aminotransferase ≥ 5 × ULN (except for isolated elevations – see below) For any dose-limiting hepatic toxicity, evaluations should be performed to determine the underlying etiology and rule out drug-induced liver injury (Hy's Law).
The following adverse events will NOT be considered DLT	Grade 3 fatigue, asthenia, anorexia, fever, or constipation Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding, total parenteral nutrition, or hospitalization Grade 3 or 4 infection, bleeding, or other expected direct complications of cytopenias due to active leukemia Grade 3 or 4 febrile neutropenia Grade 3 infusion reaction including cytokine release syndrome, if successfully managed and which resolves within 72 hours Grade 3 or 4 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage
Other adverse events not listed above	Nonhematologic toxicities of CTCAE ≥ Grade 3 are considered DLTs EXCEPT isolated Grade 3 elevations in biochemistry laboratory values without associated clinical symptoms that resolve to ≤ Grade 1 or baseline in ≤ 7 days. This includes electrolyte abnormalities that respond to medical intervention.

3.2. Treatment Assignment

3.2.1. Assignment of Patient Number

Patient numbers are assigned in sequential order as patients sign informed consent to participate.

3.2.2. Enrolled Patient Definition

Patients who have consented to the study and who have received at least 1 dose of the study drug will be considered enrolled. Patients who are issued a patient number but who do not successfully complete the screening process and/or qualify but who do not receive a dose of

study drug will be considered screen failures. Patient numbers for patients who screen fail will not be reissued.

3.2.2.1. Patient Assignment to Dose Escalation, Dose Schedule, and Dose Expansion Cohorts

Patients will be assigned to dose cohorts in both schedules in the Dose Escalation Phase and in the Dose Expansion Phase based on slot availability as determined by the Sponsor. Dose expansion cohorts may enroll concurrently. A cohort management plan will provide further details.

3.3. Dose Adjustment Criteria

3.3.1. Dose Escalation

3.3.1.1. Dose Escalation Guidelines

The planned dose levels for Schedule A will follow a modified Fibonacci dose escalation schema as outlined in Table 2. The CRC will convene after each cohort to review the collected safety, PK/Pd, and antitumor activity data (see Section 3.1.1.1). Once a DLT is observed in 1 patient, enrollment will be paused (see Section 3.1.4), and the CRC will convene and review the available safety, PK, and antileukemia activity data. Dose escalation will not proceed within that schedule during the end-of-cohort review process; the data review period for 1 schedule will not affect enrollment into a different schedule. If deemed safe to proceed, the current cohort will enroll up to 6 patients total.

PK parameters will be evaluated, and the safety and tolerability of the drug will be closely monitored.

A new dose escalation cohort within a given schedule will not open until the last patient in the enrolling cohort has completed Cycle 1 and the CRC has convened and reviewed available safety and PK data.

The dose escalation portion of the study will follow a 3 + 3 design with each cohort enrolling 3 to 6 patients until the MTD for a given schedule (Section 3.3.1.2). To allow for monitoring of severe acute toxicities, timing of dosing patients will be staggered by at least 24 hours between patients (at all dose levels during escalation). Based on emerging data, the CRC and/or Sponsor may determine whether exploration of lower or intermediate dose levels is warranted. Intermediate dose will be limited to the midpoint between previously tested doses if a difference in exposure is demonstrated between the last 2 dose levels tested.

A patient will be deemed nonevaluable for dose escalation decisions and will not be counted toward the total cohort size if the patient discontinued from the study prior to completing necessary safety evaluations through the end of the first cycle of treatment and the patient did not experience a DLT.

Nonevaluable patients will be replaced unless accrual to the cohort has stopped due to the occurrence of at least 2 patients with DLT.

3.3.1.2. Dose Escalation Rules

For patients enrolled on either schedule, dose escalation decisions will be made following a 3 + 3 design, with each cohort enrolling 3 to 6 patients. Intra-patient dose escalation will not be permitted.

- If none of the 3 patients experience a DLT, then dose escalation to the next dose level may occur.
- If 1 of the initial 3 patients experiences a DLT, the cohort will enroll up to a total of 6 patients. If no further DLT is seen, dose escalation to the next dose level may proceed.
- If at least 2 out of up to 6 patients or ≥ 33% of patients in any given cohort experience a DLT, this dose will be considered the maximum administered dose, and no further dose escalation will occur. Enrollment into a cohort at a lower or intermediate dose level may be considered.

The MTD is defined as the highest dose at which fewer than 2 of up to 6 patients or < 33% of patients experience a DLT; if, at any time, ≥ 33% of patients treated in a cohort experience a DLT, further enrollment to that cohort will stop and the CRC will be convened to review all available safety and PK data to determine how further dosing should proceed; enrollment in other ongoing cohorts may be paused at the discretion of the Sponsor.

Based on input from the CRC review of data, including PK, Pd, safety, and any signs of activity, up to 12 patients in total at a given dose level (at or below the MTD) may be enrolled to further characterize safety and identify the true DLT rate in addition to characterizing efficacy signals for either Schedule A or B.

3.3.2. Recommended Phase 2 Dose Expansion

The CRC will convene to select the dose and schedule to be used in the Dose Expansion Phase of the study. Given that IMGN632 is a targeted therapy, available information about the target along with safety, PK, and Pd data as well as antileukemia activity will be considered when selecting the optimal dose and schedule for the expansion phase. Given potential differences in sensitivity to IMGN632 between diseases and patient populations, a different RP2D or recommended schedule may be selected by the CRC based on ongoing evaluation of all available data for different expansion cohorts.

If there is evidence of late-occurring or cumulative AEs (after Cycle 1) requiring dose modification, an ad hoc CRC meeting may be scheduled to discuss dose level reduction. If agreed, the Investigators and Sponsor may increase the number of patients treated at a given dose level or enroll additional patients at the previously completed dose level to better define the safety of the study drug.

3.3.3. Dose Expansion Cohorts

Once the RP2D(s) and recommended schedule(s) are selected, the dose expansion cohorts may open. The dose expansion cohorts are designed to further evaluate safety and tolerability, assess antileukemia activity at the RP2D, and characterize IMGN632 PK. Data obtained in the Dose

Expansion Phase will help refine the RP2D. The dose expansion cohorts included in the Dose Escalation and AML/ALL/Other Expansion Phase are discussed in Section 3.1.1.2. The BPDCN Expansion Phase cohorts are discussed in Section 3.1.2.

3.3.4. Stopping Rules

The CRC will review cumulative safety data, including AEs, as well as applicable laboratory, immunogenicity and PK/Pd data, at specified intervals (see Appendix A and Appendix B) as well as on an ad hoc basis should a potential DLT be observed during the study. AEs will be assessed for relatedness to IMGN632 by the Investigators. DLTs are defined (see Table 3), and the DLT-based stopping rules for dose escalation as well as interim analyses for the BPDCN dose expansion are specified in Section 3.1.4, Section 3.3.1.2, and Section 11.1. Enrollment into the study on a given schedule will be held during the CRC data review periods of the Dose Escalation Phase (see Section 3.3.1.1). Enrollment also will be held in the case of potential DLT (see Section 3.1.4). The CRC may recommend continuing the trial if the data indicate that the DLT does not alter the current safety profile of the study drug. If the CRC should assess based on data review that the benefits of treatment with IMGN632 at a given dose or schedule do not outweigh the risks, this will result in discontinuation of any further dosing of enrolled patients and cessation of enrollment of new patients into that dose or schedule.

If at any time, the DLT rate is greater than 20% across all cohorts at the same dose level during expansion phase, further enrollment to that dose level will be closed, where the DLT occurring during any time of the study treatment period will be included.

3.4. Appropriateness of Measures

Standard statistical, clinical, and laboratory procedures will be utilized in this study and are generally accepted. All efficacy and safety-related measurements in this study are standard for assessing disease activity in patients with CD123+ malignancies.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Patient Inclusion Criteria

1. Disease characteristics:
    a. Confirmation of CD123 positivity by flow cytometry or immunohistochemistry. Patients who received prior CD123-targeting agents will be allowed as long as the blasts still have detectable CD123 expression.
    b. Dose Escalation – Relapsed/refractory AML (excluding acute promyelocytic leukemia) or BPDCN, based on World Health Organization Classification (see Appendix G for definition of clinical relapse).
    c. Dose Expansion:
        – Cohort 1 – Patients with relapsed or refractory BPDCN.
        – Cohort 2 – Patients will have relapsed AML (closed to enrollment).

- Cohort 3 – Patients will have relapsed or refractory ALL (including any subtypes: B-cell, T-cell, Ph+ and Ph-) (closed to enrollment).
- Cohort 4 – Patients will have relapsed or refractory other hematologic malignancies not included in the cohorts above (eg, high-risk/very high-risk MDS, MPN, CMML, BP-CML). Other CD123+ malignancies may be considered upon discussion with the Sponsor.

Note: BP-CML is defined as ≥ 30% blasts in blood, marrow, or both and the demonstration of extramedullary infiltrates of leukemic cells.

- Cohort 5 – Patients will have relapsed or refractory (to nonintense therapies) CD123+ AML.
- Cohort 6 – Patients with frontline de novo BPDCN at screening who have not received prior systemic therapy and patients with frontline BPDCN who have PCHM and have not received prior systemic therapy.

Note: Patients in Cohort 6 may have received local therapy (radiotherapy, surgical excision, photodynamic therapy). Eligible patients must have a recurrence or progression in the field of local therapy OR disease outside the field of local therapy. Patients identified as having concomitant malignancy while on trial will continue to be identified as de novo BPDCN patients.

2. Patients in the BPDCN Expansion Phase Cohort 1 may have received up to 3 prior lines of systemic therapy (regardless of tagraxofusp-erzs exposure).
3. Age ≥ 18 years of age.
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. If nonambulatory due to a chronic disability, must be Karnofsky performance status > 70.
5. Previous treatment-related toxicities must be resolved to Grade 1 (excluding alopecia).
6. Liver enzymes (AST and ALT) ≤ 2.5 × upper limit of normal (ULN). Exceptions may be made for patients with elevated liver transaminases secondary to the underlying study disease.
7. Total bilirubin ≤ 1.5 × ULN; patients with Gilbert syndrome must have total bilirubin < 3.0 × ULN with direct bilirubin < 1.0 × ULN at the time of enrollment.
8. An estimated glomerular filtration rate of > 30 mL/min/1.73 m^2 or creatinine clearance of > 30 mL/min.
9. Left ventricular ejection fraction ≥ 45%.
10. Patients with a prior autologous or allogeneic bone marrow transplant are eligible for Cohorts 1 through 5. Patients with an allogeneic transplant must meet the following conditions: the transplant must have been performed more than 120 days before the date of dosing on this study, the patient must not have ≥ Grade 2 acute graft versus host disease (GvHD), or extensive chronic GvHD of any severity, and must be off all immunosuppression for at least 2 weeks prior to starting treatment with IMGN632.

11. Patients or their legally authorized representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), before performance of any study-related procedure not part of normal medical care.
12. Women of childbearing potential (WCBP) patients/partners, defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months) must agree to use acceptable contraceptive methods (see Section 5.3 for details) while on study drug and for at least 7 months after the last dose of study drug.
13. WCBP must have a negative pregnancy test before the first dose of study drug.
14. Male patients/partners who are able to father children must agree to use effective methods of contraception (eg, condoms), even if they have had a successful vasectomy, throughout the study and for at least 4 months after the last dose of IMGN632.
15. Patients with prior malignancy are eligible. Patients with a PCHM are eligible as long as no current therapy is required for the second malignancy (eg, MDS, CMML). Patients with a nonhematologic prior malignancy must be in remission from the prior malignancy. Patients must have completed all chemotherapy and radiotherapy for prior malignancy at least 6 months before enrollment and all treatment-related toxicities must have resolved to Grade 1 or less.

    Note: Patients with prostate cancer or breast cancer on adjuvant hormonal therapy are eligible.

    Note: Patients with tumors with a negligible risk for metastasis or death (eg, adequately controlled basal cell carcinoma or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix or breast) are eligible.
16. Patients must not be incarcerated and must be freely willing and able to provide informed consent. Examples of patients unable to freely provide informed consent may include some adults under legal protection measure (eg, under guardianship/curatorship) or unable to express their consent and select adults under psychiatric care. Investigator's discretion should be applied.

4.2. Patient Exclusion Criteria

1. Patients who, in the judgment of their treating physician, have appropriate standard-of-care therapies will be excluded from Cohorts 1 through 5.
2. Frontline BPDCN patients with central nervous system (CNS) disease will be excluded. A lumbar puncture must be performed during the 28-day Screening period, before drug administration. Relapsed or refractory BPDCN with a known history of CNS disease must have been treated locally, have at least 1 lumbar puncture with no evidence of CNS disease, and must be clinically stable before the first dose. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is encouraged (see Section 5.2.4.1).

3. Patients with a history of veno-occlusive disease of the liver.
4. Patients with a history of Grade 4 capillary leak syndrome, or noncardiac Grade 4 edema are ineligible, eg, related to tagraxofusp-erzs or other etiology.
5. Corrected QT interval (QT interval corrected using Fridericia's formula) > 480 msec.
6. Myocardial infarction within 6 months before enrollment or has New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities before study entry.
7. Interval from prior cancer therapy:
   a. For frontline BPDCN patients with prior local therapy (eg, radiotherapy), patients must not have received treatment within 14 days before drug administration on this study.
   b. Relapsed or refractory patients must not have received any anticancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal, biologic, or any investigational agents within 14 days before drug administration on this study. Patients must have recovered to baseline from all acute toxicity from this prior therapy.
      Note: Patients who have received a checkpoint inhibitor must not have received that therapy within 28 days before drug administration on this study.
8. Clinically relevant active infection including known active hepatitis B or C, human immunodeficiency virus infection, or cytomegalovirus or any other known concurrent infectious disease that, in the judgment of the Investigator, would make a patient inappropriate for enrollment into this study (testing not required).
9. Patients who have undergone a major surgery within 4 weeks before study enrollment (or longer if not fully recovered).
10. Serious or poorly controlled medical conditions that could be exacerbated by treatment or that would seriously compromise safety assessment or compliance with the protocol, in the judgement of the Investigator.
11. Patients who are pregnant or breastfeeding.
12. Patients who have a history of allergy to IMGN632 or any of its excipients.
13. Patients who received a live vaccine four weeks or fewer prior to enrollment.

4.3. Patient Withdrawal Criteria

4.3.1. Removal of the Patients from the Study

The patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Patients may be discontinued from study drug and continue to be followed per protocol, or they may be removed from the study altogether.

4.3.2. Discontinuation from Study Drug

Patients may be withdrawn from study drug at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety or noncompliance to the protocol. Patients who meet the response criteria for PD will be removed from study drug.

4.3.2.1. Discontinuation Criteria for Individual Patients

Patients must be permanently discontinued from study drug if they meet 1 of the following discontinuation criteria:

- PD
- Study drug–related toxicities: ≥ Grade 3 cardiac events, any grade veno-occlusive disease (sinusoidal obstruction syndrome), Grade 4 nonhematologic AE, and hepatic toxicities meeting the definition of Hy's Law
  - Patients with Grade 2 veno-occlusive disease who have documented clinical benefit may be considered for additional IMGN632 dosing with Sponsor approval
- Clinical progression
- Pregnancy
- Death
- Withdrawal of consent
- Investigator decision
- Study terminated by Sponsor

Patients who permanently discontinue from study drug will enter into the follow-up phase of the study.

4.3.3. Collection of Subsequent Anticancer Treatment Information

Once a patient discontinues study drug, information regarding the subsequent anticancer therapy will be collected for all patients until either documentation of PD, the initiation of a subsequent anticancer therapy (excluding stem cell transplantation, see Section 4.4), or for up to 2 years from the time of their last dose of study drug, whichever comes first. This will include the subsequent treatment regimens and start date.

4.3.4. Reasons for Discontinuation from the Study

Reasons for patient discontinuation from the study are as follows:

- Withdrawal of consent to study treatment and follow-up
  - If a patient withdraws from the study and also withdraws consent for disclosure of future information, no further study-specific evaluations should be performed and data will no longer be collected. The Sponsor may retain and continue to use any data collected before each withdrawal of consent.
- Lost to follow-up

  - If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. Every effort should be made to document patient outcome.

- Death
- Study terminated by Sponsor

4.3.5. Replacement of Patients Who Are Withdrawn Before the End of Cycle 1

Only patients who sign the informed consent form (ICF) and receive any study drug will be considered enrolled. If an enrolled patient is discontinued from the study for reasons other than study drug–related safety (eg, withdrawal of consent, noncompliance, PD) before the end of Cycle 1, he or she will be replaced (ie, an additional patient will be added to the cohort). Patients who are replaced will not be considered in making dose escalation decisions but, if possible, will be followed for safety and other assessments according to the protocol.

4.4. Period of Observation

The period of safety observation extends from the time of signed informed consent to the study until the final safety follow-up visit.

Patients who discontinue for reasons other than PD should undergo disease assessments (Section 9.15) every 12 weeks (± 3 weeks) until documentation of PD, the initiation of a subsequent anticancer therapy (excluding stem cell transplant), or 2 years from the time of discontinuation of study drug, whichever comes first.

After documentation of PD or initiation of new anticancer therapy, the patient should be contacted every 12 weeks (± 3 weeks) for survival follow-up, including the subsequent use of anticancer therapy, and reporting of sustained response when appropriate (ie, CR, CRc, etc) for up to 2 years from the time of discontinuation of study drug, or until overall study closure.

Patients who discontinue study drug and undergo hematopoietic stem cell transplantation as consolidation will continue to be monitored for 60 days post-transplantation with information related to the transplant and any post-transplant hepatic complications recorded on the reflex transplant electronic case report form (eCRF).

5. DESCRIPTION OF STUDY DRUG

5.1. Treatment Guidelines

5.1.1. To Begin a New Cycle of Treatment

In the absence of DLTs, a patient may begin a new cycle of therapy if all nonhematologic TEAEs are ≤ Grade 2 (except alopecia and at the discretion of the Investigator) or have returned to baseline within a 2-week period, or longer with the approval of the Sponsor. See recommendations for the management of bilirubin elevation (Section 6.5.5).

5.1.2. Follow-up for DLTs and AEs Leading to Discontinuation

Patients who experience a nonlaboratory DLT must be evaluated weekly, at a minimum, until resolution to ≤ Grade 1 or baseline and then at least monthly until resolution to baseline or stabilization, whichever comes first. For abnormal laboratory values that qualify as a DLT, patients will be followed twice weekly until values return to ≤ Grade 2 or baseline, whichever comes first.

5.1.3. Criteria for Re-Initiation of Study Drug Following Occurrence of a DLT After Cycle 1

Study drug will be held if a patient experiences a DLT at any time during the study. It may resume, following dose reduction (Section 5.1.4.1) if all clinically significant, study drug-related nonhematologic TEAEs (except alopecia) have resolved to ≤ Grade 2 or returned to baseline, and after discussion with the Sponsor.

If the patient experiencing a nonhematological TEAE does not meet these criteria, dosing will be delayed, and the patient should be re-evaluated within 48 to 72 hours. Dosing may resume if these criteria have been met. However, if the next cycle is delayed by greater than 14 days because of insufficient recovery from a treatment-related nonhematologic AE, this should be reviewed with the CRC (Section 3.1.4) before re-initiation of study drug. In general, if the next cycle is delayed due to treatment-related toxicity by greater than 28 days, the patient should be removed from the study. However, the Sponsor and the Investigator may consider continuing drug administration for those patients who have experienced clinical benefit.

For hematologic TEAEs, if neutrophil and platelet counts assessed in peripheral blood samples have not resolved to ≤ Grade 2 or returned to values approximately equivalent to baseline within 28 days, a bone marrow aspirate (BMA) to assess bone marrow cellularity may be performed. Treatment should not be re-initiated if bone marrow cellularity is below 5% without evidence of leukemia.

5.1.4. Dose Modification Guidelines

5.1.4.1. Dose Reduction Following DLT

Patients who develop a DLT may continue study drug at a reduced dose level (a minimum reduction of at least 1 dose level) if the TEAE reverts to baseline or ≤ Grade 2. Dose levels are outlined in Table 2. Patients being dosed at dose level 1 who require a dose reduction should be discontinued. Dose reductions to intermediate dose levels may be allowed based on emerging data, with the approval of the Sponsor.

Once a dose level reduction has occurred, the patient must remain at this reduced dose.

5.1.4.2. Dose Reduction for Toxicities Occurring After the DLT Period

If requested by the Investigator, patients who develop a toxicity after the Cycle 1 DLT period that meets the DLT definitions in Table 3 or a dose-delaying Grade 3 or 4 toxicity may continue study drug at a reduced dose level, if the TEAE reverts to baseline or ≤ Grade 2. Patients may be allowed additional reductions with Sponsor approval. Patients being dosed at dose level 1 who require a dose reduction should be discontinued. Dose levels are outlined in Table 2; dose

reductions to intermediate dose levels may be allowed based on emerging data, with the approval of the Sponsor.

Once a dose level reduction has occurred, the patient must remain at this reduced dose.

5.1.4.3. Discontinuation of Study Drug Due to Toxicity

Study drug should not be resumed in the case of the following study drug–related events:

- ≥ Grade 3 cardiac event
- Any grade veno-occlusive disease (sinusoidal obstruction syndrome)
  - Patients with Grade 2 veno-occlusive disease who have documented clinical benefit may be considered for additional IMGN632 dosing with Sponsor approval
- Grade 4 nonhematologic AE
- Hepatic toxicities meeting the definition of Hy's Law

5.2. Concomitant Medications and Procedures

All concomitant medications and supportive therapy taken within 14 days prior to the start of Cycle 1, Day 1 and through 30 days after last dose of study drug must be recorded on the eCRF. The identity of all medications, dosage, and route of administration, frequency, duration of administration, and indication for use will be recorded on the eCRF.

The impact of cytochrome P450 (CYP) inhibitors and inducers on FGN849 is unknown. Therefore, strong inhibitors or inducers of CYP3A, CYP2D6, and CYP2C8 (Food 2020) should be avoided if possible or used with caution when medically appropriate alternatives are not available.

5.2.1. Antineoplastic Therapy

Other chemotherapy, investigational agents, or biologic therapy (including ABL inhibitors for Ph+ ALL patients) will not be permitted during study treatment. Intrathecal chemotherapy is recommended for all BPDCN patients consistent with local standard of care for patients with ALL (see Section 5.2.4.1).

5.2.2. Bisphosphonates

Bisphosphonates are permitted.

5.2.3. Granulocyte Growth Factors

The use of granulocyte growth factors is permitted at the discretion of the treating physician and per institutional guidelines.

5.2.4. Other Concomitant Medications and Procedures

Medications for the treatment of AEs or cancer symptoms (eg, packed red blood cells, pain medications, and anti-emetics) are allowed. The use of prophylactic or therapeutic antibiotics will be permitted if needed to mitigate risk of infection, at the discretion of the treating

physician. Additional medications (not addressed above) used to treat underlying medical conditions at study entry, such as anti-hypertensive, diabetes, and diuretic medications, will be allowed to continue.

Prophylactic treatment with ursodeoxycholic acid is acceptable for patients on IMGN632 treatment.

Patients should be advised to consult their treating physicians before starting treatment with herbal supplements while being treated on this study.

Receiving live vaccinations during the study and for three months after the last dose of the study drug is prohibited.

5.2.4.1. Guidance for Intrathecal Chemotherapy

The Sponsor recommends that all patients with BPDCN receive prophylactic or therapeutic CNS-directed therapy consistent with local standard of care for patients with acute lymphoblastic leukemia. The following guidelines are provided for consistency across the study, and should be followed if consistent with local standard of care:

1. For relapsed or refractory patients with CNS positivity at screening (and subsequently at least one negative LP), aggressive CNS-directed intrathecal chemotherapy is needed.
    a. Intrathecal treatments at least weekly for at least 4 doses
    b. Then, twice per month for a total of at least 8 doses
    c. Then may be continued once or twice per month, if desired
2. For all patients without CNS positivity, prophylactic CNS-directed intrathecal chemotherapy is strongly recommended.
    a. Intrathecal treatments twice per month for a total of at least 8 doses
    b. Then may be continued once or twice per month, if desired
3. Chemotherapy regimens should follow institutional standards, but would preferably be aggressive including alternating cytarabine with methotrexate, or triple intrathecals (cytarabine, methotrexate, steroid)

5.3. Acceptable Methods of Contraception

Methods that can achieve a failure rate of < 1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral

  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Permanent surgical sterilization includes methods like hysterectomy, bilateral salpingectomy, and bilateral oophorectomy for women. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRB/IEC. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study drug may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, WCBP must adhere to the contraception requirement (described above) throughout the study period and for at least 7 months after the last dose of study drug.

Male patients who are able to father children must agree to use effective methods of contraception (Section 4.1) throughout the study and for at least 4 months after the last dose of study drug. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study. Sexual partner(s) of a male patient can be exposed to the study drug. If the partner of a male patient becomes pregnant during the clinical trial, the patient and their partner will be asked to provide information about the pregnancy. All male patients must inform their partner(s) who are able to have children that the effects of the study drug on sperm are unknown.

5.4. Overdose and Medication Error

5.4.1. Overdose

There is no known treatment/antidote available for IMGN632. Supportive measures should be instituted if a patient suffers an overdose of IMGN632.

Any overdose of 10% greater than the intended dose, with or without associated AEs, and even if the AEs are nonserious, must be recorded on the applicable protocol eCRF page(s). If the overdose resulted in an SAE, an SAE form must be completed and reported to the Sponsor under

SAE timelines (Section 10.7). The event term(s) used for overdose include "overdose of IMGN632" and, if applicable, "[verbatim] secondary to IMGN632 overdose".

5.4.2. Medication Error

The Sponsor must be immediately notified in the event of error in prescribing, dispensing, administering, and/or use of IMGN632, and it must be reported on the eCRF. If an error resulted in an SAE, an SAE Form must be submitted within 24 hours of investigator awareness of the event (Section 10.7).

5.5. Treatment Compliance

The IMGN632 supplied for the study may not be used for any purpose other than the study or administered other than as described in this protocol.

Study drug from 2 different drug lots cannot be mixed in a single dose administration.

The patient's medical record must capture the dates when drug is dispensed and the initials of the person preparing the dose, as well as the volumes and doses dispensed, patient number and initials, lot number, and expiration date of the drug administered.

Under no circumstances is the Investigator allowed to release study drug supplies to any physician not named in the FDA Form 1572 (or equivalent), or to administer these supplies to a patient not enrolled in this study. If investigational supplies are to be dispensed from any facility other than that supervised directly by the Principal Investigator (ie, hospital pharmacy, satellite pharmacy), it is the responsibility of the Principal Investigator to ensure that all study drug is maintained in the manner described in this protocol and Pharmacy Manual.

5.6. Randomization and Blinding

This is an open-label, benefit-risk, study without randomization or blinding.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug

The investigational study drug, IMGN632, will be provided by the Sponsor in 20-mL glass vials as a sterile, lyophilized powder for IV infusion after reconstitution. Each vial of the drug product contains 10 mg of deliverable IMGN632 per single-use vials.

6.2. Study Drug Packaging and Labeling

IMGN632 will be provided in a 20-mL Type I clear glass vial with a dark gray Flip-off® top. Refer to the Pharmacy Manual for further information.

6.3. Study Drug Storage

Lyophilized IMGN632 should be stored upright at 2°C to 8°C. The drug vials and syringe/infusion line should be protected from light. Specific details regarding storage and handling can be found in the Pharmacy Manual.

All IMGN632 supplied for the study will be accompanied by accountability and shipping documents that must be maintained by the Principal Investigator or designee (eg, the study pharmacist). The Investigator or designee must maintain an accurate record of the receipt and dispensing of IMGN632 in a drug accountability log. These records must always be available for inspection, and a copy will be supplied to the Sponsor upon request. Information recorded on these accountability and shipping documents will include quantities received, dates and amount dispensed, initials of the person preparing dose, patient number and initials of the patient to whom the drug was administered, lot number of drug administered, and drug lost, damaged, destroyed, or returned.

Upon completion of or discontinuation from study treatment, all original study drug (containing unused study treatments) will be returned to the Sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of treatment accountability procedures. The original drug reconciliation records shall be maintained at the site and a copy collected and sent to the Sponsor once a representative of the company has witnessed the drug accountability. The pharmacy shall maintain accurate records of all study drugs that have been received, stored, dispensed, destroyed, and used. The eCRF shall also record details of IMGN632 administration such as date and time of administration.

Drug accountability will be monitored regularly.

6.4. Study Drug Preparation

6.4.1. Premedication

Patients must receive the following premedication on the day *before* any IMGN632 dose:

- 8 mg dexamethasone (per os [PO] or IV) BID

Patients must receive the following premedication regimen before each IMGN632 infusion:

- 25 to 50 mg diphenhydramine (IV) and
- 325 to 650 mg acetaminophen or paracetamol (IV or PO) and
- 8 mg dexamethasone (IV) or equivalent

If individual patients require more intensive or alternative treatment to prevent infusion reactions (eg, a different corticosteroid, different dose of any agent), Investigators may modify the regimen according to standard institutional practice.

6.4.2. Preparation

Doses will be calculated based on actual body weight. If weight is not collected per the frequency described in Appendix A, Appendix B, or Appendix C for any reason, the most recent

weight should be used for dose calculation unless the weight increase is attributed to fluid retention. Lyophilized IMGN632 should be reconstituted using 5.4 mL of water for injection, and then administered as outlined in the Pharmacy Manual.

Note: IMGN632 is incompatible with saline (0.9% sodium chloride). Therefore, flushing must be made using 5% dextrose.

IMGN632 contains no bacteriostatic preservatives, and the reconstituted solution should be used immediately. Reconstituted IMGN632 in the current formulation is sensitive to light. Exposure to high intensity light (ie, UV light sources and direct sunlight) must be avoided. Exposure to light of normal (ambient) intensity (ie, less than 1000 lux) should be limited to a maximum of 8 hours from the time of reconstitution to beginning of infusion.

6.5. Administration

IMGN632 will be administered by IV syringe pump following preparation as outlined in the Pharmacy Manual.

The overall length of infusion will vary depending on dose and patient tolerability. Initially, the study drug should be administered at a rate of 0.165 mg/min; after 30 minutes, and if well tolerated, the rate may be increased to 0.33 mg/min. Subsequent infusions may be delivered at the highest tolerated rate. Before and following infusion, the line should be flushed with 5% dextrose to ensure delivery of the full dose.

Patients will be carefully observed during each infusion and vital signs taken as outlined in the schedules of assessments (Appendix A, Appendix B, and Appendix C). Patients will remain in the clinic under observation for 4 hours after the first infusion and for at least 1 hour after each subsequent infusion.

6.5.1. Dose Escalation and AML/ALL/Other Expansion Phase

Patients enrolled in Schedule A will receive IMGN632 on Day 1 of a 21-day cycle. The starting dose of IMGN632 for patients enrolled in the Dose Escalation Phase will be 0.015 mg/kg.

Patients enrolled in Schedule B will receive IMGN632 on Days 1, 4, and 8 of a 21-day cycle. The starting dose for Schedule B will be determined by the CRC based on safety, Pd, and PK data, with a maximum starting dose in equal fractions of the last dose cleared on Schedule A (eg, 1/3 of the total dose administered on Schedule A on each of Days 1, 4, and 8).

6.5.2. BPDCN Expansion Phase

Patients enrolled in the BPDCN Expansion Phase will receive IMGN632 on Day 1 of a 21-day cycle. The dose of IMGN632 will be 0.045 mg/kg.

6.5.3. Management of IMGN632 Infusion-Related Reactions

Infusion reactions may occur with ADCs, including IMGN632. Infusion-related reactions (nonserious and serious) are AESI and must be reported using an SAE form per Section 10.4.2.

Before any infusion is started, appropriate medical personnel, medication (eg, epinephrine, inhaled beta-agonists, antihistamines, and corticosteroids), and other required resources to treat

anaphylaxis must be readily available. To monitor for potential infusion-related reactions, vital signs are recommended to be assessed within 30 minutes prior to dose and approximately every 15 minutes (or as indicated by institutional practice) for at least 1 hour following infusion. For the first infusion of IMGN632, additional assessments will be performed approximately every 30 minutes for at least 4 hours, or longer as clinically indicated. In general, Investigators should manage acute hypersensitivity reactions according to institutional practices.

General guidelines for management of acute reactions and subsequent retreatment with IMGN632 are provided in Table 4. The guidelines for management of infusion reactions are suggested approaches; variations are allowed to accommodate institutional guidelines/practices. Infusion–related reactions may recur after appropriate treatment; therefore, patients should be advised to seek immediate medical treatment if symptoms recur after discharge from clinic.

Patients who experience a Grade 2 or greater infusion-related reaction following administration of IMGN632 will have blood drawn for determination of drug concentration and antibodies to IMGN632 (ADA). The sample should be obtained within 3 hours of the onset of the reaction and 1 week later. Such patients should undergo all scheduled antileukemia activity and safety evaluations.

Table 4: Management Guidelines for Infusion Reactions

Infusion Reaction CTCAE v4.03 Grade	**Management**[a]
Grade 1: Mild, transient reaction	• Maintain infusion rate unless progression of symptoms to ≥ Grade 2; if symptoms worsen, refer to guidelines below • Promethazine (or equivalent) 150 mg PO per day (25 mg every 4 hours) prn for nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Methylprednisolone 125 mg (or equivalent) IV prn • Monitor vital signs approximately every 15 minutes (or as indicated by institutional practice) for at least 1 hour following reaction, with continuing assessment as clinically indicated until full resolution
Grade 2: Moderate	• Interrupt infusion and disconnect infusion tubing from patient (if applicable) • Promethazine (or equivalent) 150 mg per day (25 mg every 4 hours) PO prn nausea • Diphenhydramine (or equivalent) 25-50 mg PO or IV prn • Acetaminophen (or equivalent) 650 mg PO prn • Methylprednisolone 125 mg (or equivalent) IV prn • Monitor vital signs approximately every 15 minutes (or as indicated by institutional practice) for at least 1 hour following reaction, with continuing assessment as clinically indicated until full resolution • After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed

Table 4: Management Guidelines for Infusion Reactions (Continued)

Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	• Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine (25-50 mg) IV • Administer normal saline, epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) subcutaneously or intramuscularly), and bronchodilators (nebulized albuterol, 2.5-5 mg in 3 mL of saline) as medically indicated • Consider IV steroids (methylprednisolone [or equivalent] up to 0.5 mg/kg every 6 hours) to prevent recurrent or ongoing reactions • Monitor vital signs approximately every 15 minutes (or as indicated by institutional practice) for at least 4 hours following reaction, with continuing assessment as clinically indicated until full resolution. • If the infusion-related symptoms recur after discharge from clinic, advise patient to seek emergency treatment and notify the Investigator/clinic • Report as an SAE (see Section 10.7) • Investigators should confer with the Sponsor regarding retreatment of the patient with IMGN632. If the Investigator and Sponsor agree that the patient may be rechallenged with IMGN632, prophylaxis for an infusion-related reaction should occur in all subsequent cycles (see Section 6.4.1).
Grade 4: Life-threatening consequences, urgent intervention indicated	• Immediately stop infusion and disconnect infusion tubing from patient • Permanently discontinue study medication treatment • Administer diphenhydramine (or equivalent) 50 mg IV • Administer normal saline, epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) subcutaneously or intramuscularly) • Administer bronchodilators (nebulized albuterol, 2.5-5 mg in 3 mL of saline) as medically indicated • Administer IV steroids (methylprednisolone (or equivalent) up to 0.5 mg/kg every 6 hours) to prevent recurrent or ongoing reactions • Monitor vital signs approximately every 15 minutes (or as indicated by institutional practice) for at least 4 hours following reaction, with continuing assessment as clinically indicated until full resolution. • Report as an SAE (see Section 10.7) • Remove patient from study

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = by mouth; prn = as needed; SAE = serious adverse event.
[a] Presented as suggested approaches. Not meant to replace clinical judgment or institutional guidelines/practices.

6.5.4. Management of Tumor Lysis Syndrome

Patients experiencing tumor lysis syndrome will be managed according to institutional practice. This may include prophylaxis with rasburicase and hydration in high-risk patients, allopurinol or rasburicase and hydration in intermediate-risk patients, and close monitoring for low-risk patients (Coiffier 2008). Primary management for tumor lysis syndrome includes similar measures, together with aggressive hydration and diuresis and allopurinol or rasburicase for hyperuricemia.

6.5.5. Management of Liver Adverse Events

Several cases of veno-occlusive disease of the liver (sinusoidal obstruction syndrome) have been observed in patients with monotherapy IMGN632. For details, please refer to the Investigator's Brochure. Please closely monitor patients for liver toxicity.

Table 5: Management of Liver Adverse Events

Liver Adverse Event	Recommendation
If total bilirubin is Grade 1 (> ULN to 1.5 × ULN)	Obtain fractionated bilirubin Consider prophylaxis with ursodeoxycholic acid and/or steroids if at risk for VOD
If total bilirubin is Grade ≥ 2 (> 1.5 × ULN)	Obtain fractionated bilirubin Etiologies for hyperbilirubinemia should be explored, including VOD. Prophylaxis with ursodeoxycholic acid and/or steroids are strongly recommended **Further dosing with IMGN632 must be delayed until total bilirubin has returned to Grade 0-1 (≤ ULN to 1.5 × ULN), and Sponsor approval is obtained**
If either AST or ALT is > 3× ULN	Obtain total and fractionated bilirubin Etiologies for transaminitis should be explored, including VOD Consider prophylaxis with ursodeoxycholic acid and/or steroids if at risk for VOD **Further dosing with IMGN632 must be delayed until both AST and ALT have returned to ≤ 3 × ULN**
If any Grade VOD is diagnosed (see CTCAE v5)	**IMGN632 should be permanently discontinued for any grade VOD** However, patients with Grade 2 VOD and documented clinical benefit may receive further dosing following Sponsor approval (Section 4.3.2.1)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal; VOD = veno-occlusive disease.

6.5.6. Fluid Retention/Peripheral Edema

Fluid retention, primarily in the form of peripheral edema, has been observed in approximately one third (31%) of patients, and can progress to Grade 3 in approximately 5% of patients. Edema in patients treated with IMGN632 appears to be correlated with higher body weight and higher body mass index. Monitor patients frequently for weight gain as a sign of fluid retention. Edema in some patients has been furosemide-refractory, consider early and more aggressive treatment than routine edema. Refer to Table 6 for management of edema. Also consider a course of steroids and/or ursodeoxycholic acid if inflammation and/or veno-occlusive disease are concerns (Essell 1998, Ohashi 2000).

Table 6: Management of Edema

Edema Adverse Event	Recommendation
If edema is Grade 1 (5% to 10% inter-limb discrepancy in volume or circumference) Or > 5 lb (> 2 kg) ≤ 10 lb (4 kg) weight gain Or 1+ pitting edema (2 mm)	Follow weights weekly as described in the schedule of assessments (Appendix A and Appendix C) Elevation/compression stockings Consider outpatient diuretic therapy (furosemide, other)
If edema is Grade 2 (> 10% to 30% inter-limb discrepancy in volume or circumference; readily apparent obscuration of anatomic architecture; limiting instrumental ADL) Or > 10 lb (4 kg) weight gain Or 2+ pitting edema (4 mm)	Follow weights weekly, as noted in the schedule of assessments (Appendix A and Appendix C) Treat with potent diuretic therapy. Consider diuretic combinations (spironolactone or metolazone or amiloride) or increased potency diuretic therapy (bumetanide (Bumex), torsemide) Treat hypoalbuminemia **Further dosing with IMGN632 must be delayed until edema has returned to Grade 0-1 or baseline** **If delayed past 2 weeks, consider dose reduction before resuming IMGN632 dosing after consult with Sponsor**
If edema is Grade 3 (> 30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL) Or 3+/4+ pitting edema (> 6 mm)	Follow weights weekly, as described in the schedule of assessments (Appendix A, Appendix B, and Appendix C) Recommend diuretic combinations (spironolactone and/or metolazone and/or amiloride and/or hydrochlorothiazide) and/or increased potency diuretic therapy (bumetanide (Bumex), torsemide) Treat hypoalbuminemia **Further dosing with IMGN632 must be delayed until edema has returned to Grade 0-1 or baseline** **Patients must resume IMGN632 at 1 lower dose level after consult with Sponsor**
If edema is Grade 4 (life threatening)	Treat per local practice for life-threatening edema **Must discontinue IMGN632 treatment but should remain on study for follow up of safety and response (Section 4.4)**

6.5.7. Study Drug Handling and Disposal

IMGN632 is an experimental anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling this compound. It is recommended that gloves and protective garments be worn during preparation. Please see the Pharmacy Manual for additional information on study drug handling and disposal.

7. PK AND IMMUNOGENICITY ASSESSMENTS

7.1. PK Assessments

Blood samples will be taken to assess the PK properties of IMGN632. Samples will be analyzed for levels of IMGN632, total antibody, and FGN849 (active catabolite). Details of sample preparation and shipping are provided in the Laboratory Manual. If possible, blood transfusions should be avoided on the same day of IMGN632 dosing and be delayed to the following day.

7.1.1. Dose Escalation and AML/ALL/Other Expansion Phase

For the revised PK schedule for the BPDCN Expansion Phase, please see Section 7.1.2.

Blood samples for PK measurements will be taken, for all patients, at the following timepoints (Appendix D and Appendix E):

Schedule A

- ***Cycles 1 and 3***
  - Day 1: pre-dose and immediately following the completion of infusion of IMGN632 (+ 10 minutes), at 2 hours (± 10 minutes), 4 hours (± 15 minutes), and 6 hours (± 1 hour)
  - Day 2: 24 hours after the completion of the IMGN632 infusion (± 4 hours)
  - Day 3: 48 hours after the completion of the IMGN632 infusion (± 6 hours)
  - Day 8: 168 hours after the completion of the IMGN632 infusion (± 24 hours)
  - Day 15: 336 hours after the completion of the IMGN632 infusion (± 24 hours)
- ***Cycle 2 and Cycles 4 through 6***
  - Day 1: pre-dose and immediately following the completion of the IMGN632 infusion (+ 10 minutes)
- ***Unscheduled Visit***
- ***End of Treatment Visit***
- ***30-Day Follow-up***

NOTE: Patients who experience a Grade 2 or greater infusion-related reaction following administration of IMGN632 will have blood drawn for determination of drug concentration and antibodies to IMGN632. The sample should be obtained within 3 hours of the onset of the reaction and again 1 week later. PK samples may also be obtained as feasible any time during the treatment period for assessment of study drug-related SAEs if deemed appropriate by the Investigator and Sponsor.

Schedule B

- ***Cycles 1 and 3***
  - Day 1 Dose 1: pre-dose and immediately following the completion of infusion of IMGN632 (+ 10 minutes)
  - Day 4 Dose 2: pre-dose and immediately following the completion of infusion of IMGN632 (+ 10 minutes)
  - Day 8 Dose 3: pre-dose and immediately following the completion of infusion of IMGN632 (+ 10 minutes), at 2 hours (± 10 minutes), 4 hours (± 15 minutes), and 6 hours (± 1 hour)
  - Day 9: 24 hours after the completion of the Day 8 infusion (± 4 hours)
  - Day 10: 48 hours after the completion of the Day 8 infusion (± 6 hours)
  - Day 15: 168 hours after the completion of the Day 8 infusion (± 24 hours)
- ***Cycle 2 and Cycles 4 through 6***
  - Day 1 Dose 1: pre-dose and immediately following the completion of the IMGN632 infusion (+ 10 minutes)
  - Day 4 Dose 2: pre-dose and immediately following the completion of the IMGN632 infusion (+ 10 minutes)
  - Day 8 Dose 3: pre-dose and immediately following the completion of the IMGN632 infusion (+ 10 minutes)
- ***Unscheduled Visit***
- ***End of Treatment Visit***
- ***30-Day Follow-up***

NOTE: Patients who experience a Grade 2 or greater infusion-related reaction following administration of IMGN632 will have blood drawn for determination of drug concentration and antibodies to IMGN632. The sample should be obtained within 3 hours of the onset of the reaction and again 1 week later. PK samples may also be obtained as feasible any time during the treatment period for assessment of study drug–related SAEs if deemed appropriate by the Investigator and Sponsor.

7.1.2. BPDCN Expansion Phase

As of Amendment 6.0, blood samples for PK measurements will be taken, for all patients, at the following timepoints (Appendix F):

[redacted]

[redacted]

7.2. Immunogenicity Assessments

The potential immunogenicity against IMGN632 will be assessed in samples collected pre-dose, at the End of Treatment, and at 30-Day Follow-up visits as outlined in Appendix D, Appendix E, and Appendix F. ADA will be evaluated in blood samples collected for PK assessments collected on Day 1 of Cycles ≤ 4, End of Treatment, and at 30-Day Follow-up visits; no additional sample collections are necessary. For Cycle 5 and beyond, a blood sample for ADA will be drawn on Day 1 of each cycle. Immunogenicity data will be explored to assess its potential impact on PK, safety, and antileukemia activity of IMGN632 [redacted] (Section 11.4).

7.3. Future Use of PK and Immunogenicity Samples

For patients who consent to it, leftover samples following PK and immunogenicity testing may be used for other research purposes (excluding genetic analysis). These other research analyses will help to understand either AML disease subtypes or drug responses, to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers. These samples will remain labeled with the same identifiers used during the study (ie, patient ID). They will be transferred to the Sponsor (or a subcontractor site), which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentially and personal data (see Section 12.4).

8. TRANSLATIONAL RESEARCH STUDIES

Translational research studies will be performed to characterize Pd and evaluate potential predictive biomarkers of clinical response to IMGN632. These data may help guide further clinical development of IMGN632. The analysis and subsequent results of these assessments may be reported in separate documents and not included in the SAP or Clinical Study Report, respectively.

8.1. Clinical Sample Collection for Biomarker Testing

BMA and blood samples will be collected according to the schedule outlined in Appendix D, Appendix E, and Appendix F. Details of sample preparation and shipping will be provided in the Laboratory Manual.

[redacted]

8.4. Future Use of Biomarker Samples

For patients who provide consent, leftover blood and bone marrow samples after biomarker testing may be used for other research purposes. These other research analyses will help to understand either AML disease subtypes or drug responses, to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers. These samples will remain labeled with the same identifiers used during the study, ie, patient ID. They will be transferred to the Sponsor (or a subcontractor site), which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 12.4).

9. STUDY PROCEDURES

9.1. Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted (Appendix C), unless those procedures are performed as part of the patient's standard care.

If an amendment substantially alters the trial design, increases the potential risk to the patients, affects the treatment of the patient, or might otherwise influence the willingness of the patient to participate in the trial, then the ICF must be revised and submitted to the relevant IRB/IEC and, where necessary, to the relevant competent authorities, for review and approval. When a patient is currently undergoing trial procedures and is affected by the amendment, then the patient must be asked to consent again using the new ICF.

9.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening (within 28 days prior to the first dose of any study drug on Cycle 1, Day 1, or as otherwise specified [Appendix C]). A patient is considered enrolled when administered the first dose of study drug.

Procedures for completion of enrollment information, and requirements to communicate with the Sponsor about enrollment, are detailed in the Study Manual.

Note: Pulmonary function test will not be required. Pulmonary function test results, including diffusing capacity for carbon monoxide if known, may be used to determine eligibility.

9.3. Confirmation of Disease Diagnosis

At screening, disease diagnosis and current disease status will be confirmed from information in the source record.

9.4. Demographic/Medical History

The age and gender of the patient are to be recorded during screening.

During the Screening period, a complete medical history will be compiled for each patient. The history will include the background and progress of the patient's primary malignancy, medical history, baseline signs, and symptoms, and will include a description of all prior cancer therapies.

9.5. Lumbar Puncture

Lumbar puncture is to be performed as indicated in the schedule of assessments for patients in the BPDCN Expansion Phase (Appendix C). As outlined in the exclusion criteria, all patients with a known history of CNS disease must have been treated locally, have at least 1 lumbar puncture with no evidence of CNS disease, and must be clinically stable prior to first dose (Section 4.2).

9.6. Physical Examination and Height

Physical examination and height (screening only) are to be performed as indicated in the schedule of assessments (Appendix A, Appendix B, and Appendix C). A complete physical examination will be completed at screening and end of treatment. Symptom-directed physical examinations will be completed at additional timepoints as specified in the schedule of assessments.

9.7. Vital Signs and Weight

Body weight and vital signs, including blood pressure, heart rate, temperature, and respiratory rate, will be measured at the times specified in the schedule of assessments (Appendix A, Appendix B, and Appendix C).

9.8. Electrocardiogram

9.8.1. Dose Escalation and AML/ALL/Other Expansion Phase

A single, standard 12-lead ECG will be performed within 14 days prior to first dose. A single ECG will also be performed at the End of Treatment visit and as clinically indicated (Appendix A and Appendix B).

Schedule A:

On-study ECGs will be performed <u>in triplicate</u> at 2- to 5-minute intervals at the following timepoints:

- Pre-dose ECG: on **<u>Day 1 of every cycle</u>**, within 1 hour before dosing
- Post-dose ECGs (**<u>Cycle 1 ONLY</u>**):
  - At the end of infusion on Day 1 to coincide with C_{max} and PK blood draw (within 30 minutes from this blood draw).
  - 24 ± 2 hours (Day 2) and 48 ± 2 hours (Day 3) post infusion to coincide with PK blood draw.

Schedule B:

On-study ECGs will be performed <u>in triplicate</u> at 2- to 5-minute intervals at the following timepoints:

- Pre-dose ECG: on **<u>Cycle 1, Day 1</u>**, within 1 hour prior to dosing
- Pre-dose ECG: on **<u>Cycle 1, Day 8</u>**, within 1 hour prior to dosing
- Post-dose ECGs (**<u>Cycle 1 ONLY</u>**):
  - At the end of infusion on Day 8 to coincide with PK blood draw (within 30 minutes from this blood draw).
  - 24 ± 2 hours (Day 9) and 48 ± 2 hours (Day 10) post Day 8 infusion to coincide with PK blood draw.

On-study single ECGs will be performed at the following timepoints:

- Pre-dose ECG: on **<u>Day 1 of every cycle</u>**, within 1 hour prior to dosing

9.8.2. BPDCN Expansion Phase

A single, standard 12-lead ECG will be performed within 14 days prior to the first dose. A single ECG will also be performed at the End of Treatment visit and as clinically indicated (Appendix C).

On-study ECGs will be performed <u>in triplicate</u> at 2- to 5-minute intervals at the following timepoints:

[redacted]

Printed, de-identified, and signed copies of all ECGs taken throughout the study should be batched and mailed to the Sponsor, together with the ECG submission form using the address provided in the form.

9.9. Left Ventricular Ejection Fraction Assessment

Echocardiogram (or other cardiac testing modality) will be performed within 28 days prior to first dose to ensure that patients meet the left ventricular ejection fraction threshold required for enrollment in the study as clinically indicated. If repeated after screening, the same test should be performed throughout the trial (Appendix A, Appendix B, and Appendix C).

9.10. Bone Marrow Aspirate

A BMA will be performed during the Screening period or on Cycle 1, Day 1 prior to first dose. Existing bone marrow results may be used if within the 28-day screening window (Appendix C). Response assessments by BMAs for differential assessments will be made at the end of Cycles 1, 2, 4, and 6, then every 4 cycles thereafter (approximately every 3 months, Table 8). BMAs will not be required if there is presence of circulating blasts.

When a bone marrow sample is taken for response assessments, a portion is requested for biomarker testing and a portion for genomics testing at timepoints specified in Appendix D, Appendix E, and Appendix F. Biomarker and genomics testing are exploratory, and a specific bone marrow aspirate is not required.

9.11. CT/PET Scan (Cohort 1; BPDCN Patients Only)

9.11.1. Dose Escalation

CT/PET scans will be performed within 28 days prior to the first dose to ensure the patient meets eligibility. Existing CT/PET scans may be used if within the 28-day screening window. For the screening scan, a general description of disease involvement and specific identification of up to 6 index lesions with 2 dimensions measured for each lesion is to be provided. CT/PET scans may be performed any time within ± 1 week of Cycle 3, Day 1 if clinically indicated and in subsequent cycles as clinically indicated. For subsequent CT/PET scans, a general description of disease involvement with specific comment if new lesions are present, specific comment about whether there is an increase in size of the spleen and liver with dimensions, and specifics comparison of the same up to 6 index lesions noting their new 2 dimensions (and change in standard uptake values if possible) is to be provided. Please refer to CT/PET scan instructions (Appendix K) for further details.

9.11.2. BPDCN Expansion Phase

For BPDCN patients, CT/PET scans will be performed within 28 days prior to the first dose to ensure the patient meets eligibility. Existing CT/PET scans may be used if within the 28-day screening window (Appendix C). For the screening scan, a general description of disease involvement and specific identification of up to 6 index lesions with 2 dimensions measured for each lesion is to be provided. Nodal/visceral involvement will be assessed by CT/PET after the end of Cycles 2, 4, and 6, and at the end of every 4 cycles thereafter (Table 8). Following

establishment of response, repeated CT/PET scans will only be required on patients with nodal/visceral disease at baseline, or as indicated clinically. Patients with baseline nodal/visceral disease will still be required to have CT/PET after a response is established. For subsequent CT/PET scans, a general description of disease involvement with specific comment if new lesions are present, specific comment about whether there is an increase in size of the spleen and liver with dimensions, and specifics comparison of the same up to 6 index lesions noting their new 2 dimensions (and change in standard uptake values if possible) is to be provided. Please refer to CT/PET scan instructions (Appendix K) for further details.

9.12. Skin Assessment (mSWAT/Biopsy)

For BPDCN patients with skin lesions, skin assessments will be performed within 28 days prior to the first dose, and photographs will be taken if the patient has viable lesions. An existing biopsy of BPDCN skin lesions may be used if within the 28-day screening window (Appendix C). Skin involvement will be assessed by photographs and Modified Severity-Weighted Assessment Tool (mSWAT) at the end of Cycle 1 and 2, and at the end of every 2 cycles thereafter (approximately every 6 weeks, Table 8). A biopsy of normal-appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a CR would exist.

9.13. Laboratory Assessments

Patients should be in a seated or supine position during blood collection. Screening laboratory assessments (hematology, clinical chemistry, and urinalysis) are to be performed within 14 days prior to enrollment. Day 1 laboratory assessments may be performed up to 3 days prior to study drug administration. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 3 days of dosing and are within acceptable ranges. Repeat testing will be performed as outlined in schedules of assessments (Appendix A, Appendix B, and Appendix C) and as clinically indicated.

Note that prior to each administration of IMGN632, laboratory results must be reviewed to evaluate for potential toxicity. For patients where dosing is delayed, it is important to record any clinically relevant laboratory results obtained on non-trial mandated visit days in an unscheduled visit eCRF.

Clinical laboratory tests will include those listed in Table 7:

Table 7: Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation Tests[a]	Urinalysis	Other
Hemoglobin WBC (with 5-part differential) Platelet count ESR or equivalent[b] vWF[b]	Albumin Alkaline phosphatase ALT AST BUN Calcium Chloride Creatinine Glucose LDH Magnesium Phosphorus Potassium Sodium Total bilirubin Direct bilirubin[c] Uric acid	PT aPTT INR	pH Ketones Protein Glucose Occult blood Leukocyte esterase Nitrite (microscopic examination of sediment must be performed if any urinalysis dipstick results are positive)	β-hCG (serum or urine)

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; ESR = erythrocyte sedimentation rate; INR = international normalized ratio; LDH = lactic acid dehydrogenase; PT = prothrombin time; vWF = von Willebrand Factor; WBC = white blood cell count.

[a] Coagulation tests are to be performed at screening only and as clinically indicated.

[b] ESR (or equivalent) and vWF are to be performed prior to each IMGN632 dose (Day 1) and 7 days post dose (Day 8) of each cycle, if these tests are available.

[c] Direct bilirubin is to be collected only if ALT, AST, or total bilirubin is elevated (Table 5).

9.13.1. Pregnancy Screen

All WCBP will complete a serum beta-human chorionic gonadotropin (β-hCG) test not more than 3 days before the first dose of IMGN632; this test must be negative for the patient to be enrolled and to receive the study drug. A urine or serum pregnancy test will be performed every other cycle while on study and at the 30-Day Follow-up visit (Appendix C). Additional testing may be performed in accordance with institutional requirements or local regulation.

If a patient becomes pregnant or suspects pregnancy while participating in this study, the Investigator and Sponsor must be informed immediately, and the patient will be withdrawn from the study.

9.13.2. Urinalysis

- Specific gravity and pH
- Semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood

- Microscopic examination of sediment must be performed if any urinalysis dipstick results are positive

9.13.3. Coagulation

- Prothrombin time or international normalized ratio
- Activated partial thromboplastin time

9.14. ECOG Performance Status

ECOG performance status (Appendix J) will be assessed during screening and at other times specified in the schedules of assessments (Appendix A, Appendix B, and Appendix C). An assessment is not necessary on Cycle 1, Day 1 if the screening assessment was obtained within 3 days prior to Day 1. For patients who are not ambulatory due to a chronic condition, the Karnofsky score may be used.

9.15. Disease Response Assessment

9.15.1. Dose Escalation and AML/ALL/Other Expansion Phase

Response assessments will be performed in BMAs for differential assessments taken on Cycle 1, Day 21 ± 7 days. Subsequent BMAs should be performed approximately every 1 to 2 cycles as clinically indicated, and at the 30-Day Follow-up visit. Data will also be collected in the event that BMAs are performed more frequently. No repeat bone marrow is necessary if lack of response or PD can be unequivocally diagnosed from peripheral blood tests or if the bone marrow test is considered noncontributory by the Investigator at any timepoint.

[redacted]

Hematologic response for all patients will be assessed using the applicable standard-of-care response criteria for leukemia, lymphoma, MDS/MPN, or mastocytosis (Appendix F, Appendix H, Döhner 2017, Cheson 2007, Gotlib 2013, Savona 2015).

The mSWAT criteria (Appendix I, Olsen 2011) should be used for skin assessment, scoring, and definition of response as applicable for BPDCN patients.

9.15.2. BPDCN Expansion Phase

[redacted]

[redacted]

Table 8: BPDCN Expansion Phase Disease Assessment Schedule

Assessment	[redacted]
Bone marrow aspirate	
CT/PET scan[a]	
Skin mSWAT[b,c]	

CR = complete response/remission; CT/PET = computed tomography/positron emission tomography; mSWAT = Modified Severity-Weighted Assessment Tool.

[a] CT/PET scans are to be performed for all patients on this schedule until CR is achieved then CT/PET will only be required for those patients with baseline nodal/visceral involvement.

[b] A biopsy of normal-appearing skin is unnecessary to assign a CR. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a CR would exist.

[c] Photographs of skin lesions will be taken by Investigator or designee.

9.15.3. Recurrence of Disease

Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the BMA not attributable to any other cause or reappearance or new appearance of extramedullary leukemia (Appendix H). Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the BMA to > 25% not attributable to any other cause or reappearance or new appearance.

9.15.4. Best Response Determination

Best response is defined to be the best documented response (CR_{MRD-}, CR, CRh, CRi, CRc [redacted] MLFS, hematologic improvement [for other hematologic malignancies], PR, stable disease [SD], PD) post-treatment, up to that time. Best response will also be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

9.16. Eligibility Based on CD123 Expression

All patients will be screened to ensure that they have CD123+ malignancies, as determined by flow cytometry or immunohistochemistry by the investigational sites in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. [redacted]

10. ASSESSMENT OF SAFETY

The safety profile of IMGN632 will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings, laboratory tests, and vital sign data. Comprehensive assessment of any toxicity experienced by the patient will be performed throughout the course of the trial, whether observed by the Investigator or reported by the patient.

The Investigator should take appropriate measures to follow and provide updates for all AEs until clinical recovery is complete, laboratory values return to normal, the patient stabilizes, or death occurs. This may mean that observations continue beyond the last planned visit per protocol and that additional investigations may be requested by the Sponsor.

10.1. Baseline Medical Conditions

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as "Baseline Medical Conditions" and are NOT AEs in and of themselves. These medical conditions should be documented on the appropriate page of the eCRF (eg, medical history page).

However, a medical condition present at the initial study visit that worsens in severity or frequency during the study should be recorded and reported as an AE.

10.2. Progression of Disease

In this protocol, worsening or progression of relapsed/refractory CD123+ AML and other CD123+ hematologic malignancies are efficacy criteria and are recorded on applicable pages of the eCRF. Therefore, worsening or PD is not considered an event term, and will therefore not be captured on the AE eCRF unless the sign/symptom/diagnosis is untoward for a given patient and/or disease state.

If a patient expires from PD during the reporting period, the same rule applies. The death should not be reported as a SAE term unless the course/nature was untoward. The applicable protocol eCRF page(s) pertaining to death (End of Treatment, End of Study, Death eCRF) should be completed per eCRF completion guidelines.

10.3. Time Period for Recording AEs

10.3.1. Recording

All AEs occurring from informed consent until 30 days after last study drug administration must be recorded on the AE eCRF, regardless of the seriousness, severity, or relationship to study drug.

However, beyond the reporting period, any unsolicited SAE assessed as related to IMGN632 by the Investigator and received by the Sponsor will be processed and reviewed.

10.3.2. Follow-up

All AEs should be reported on the AE eCRF until 30 days after the patient's last administration of study drug. The investigator should follow and provide updates for all AEs until clinical recovery is complete, returned to baseline, laboratory values return to baseline, the patient stabilizes, or death occurs.

For patients who undergo hematopoietic stem cell transplantation as consolidation following the discontinuation of IMGN632, hepatic-related safety information is to be recorded on the reflex transplant eCRF for 60 days post-transplantation.

10.4. Definition: Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug related. This includes an exacerbation of a pre-existing condition. AEs can also include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events possibly related to concomitant medications
- Clinically significant abnormalities in physical examination, vital signs, and weight

The Investigator should treat AEs appropriately and observe them at suitable intervals until the events stabilize, return to baseline, or resolve.

10.4.1. Abnormal Laboratory Findings and Other Objective Measurements

All AEs will be followed and eCRFs updated until event resolution or until 30 days after last study drug administration, whichever comes first.

However, SAEs will be followed by the Sponsor's Pharmacovigilance team until resolution, stabilization, or return to baseline, regardless of study status or time since last IMGN632 administration.

If reporting an abnormal laboratory finding as an AE, a clinical diagnosis should be recorded rather than the abnormal value itself, if available (eg, "anaemia" rather than "decreased red blood cell count" or "hemoglobin = 105 g/L").

10.4.2. Adverse Events of Special Interest

IMGN632 has 1 AESI: infusion-related reaction. Any symptom or sign occurring within 24 hours of infusion and suggestive of an infusion-related reaction should be promptly reported per Section 10.7.

10.5. Definition: Serious Adverse Event

An SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intense treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

10.6. Investigator Assessment of Adverse Events

All AEs will be assessed for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (effective 14 June 2010). If the AE is not listed in the CTCAE version 4.03, it should be graded based on the qualitative scale provided in Table 9.

Table 9: Adverse Event Severity

Severity	Definition
Grade 1 (Mild)	No limitation of usual activities
Grade 2 (Moderate)	Some limitation of usual activities
Grade 3 (Severe)	Inability to carry out usual activities
Grade 4 (Life-threatening)	Immediate risk of death
Grade 5 (Fatal)	Resulting in death

All AEs will be assessed for relationship to study drug based upon the definitions listed in Table 10.

Table 10: Relationship to Study Drug

Relationship to Study Drug	Definition
Not Related	A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.
Unlikely Related	A temporal relationship to study drug administration exists which makes a causal relationship improbable, and another documented cause is most probable.
Possibly Related	A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of study drug.
Probably Related	A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, and there is a reasonable response upon withdrawal of study drug.
Definitely Related	A causal relationship is clinically/biologically highly plausible, occurred in a plausible time relationship to study drug administration, and the event cannot be explained by concurrent disease or other drugs or chemicals.

10.7. Reporting SAEs and AESIs

Any SAE, regardless of relationship to study medication, that occurs in a patient from time of informed consent until 30 days after the last dose of study drug, must be recorded by the clinical site on an SAE report form and monitored until the event has resolved, stabilized, or an outcome has been reached, whichever comes first. This reporting requirement also includes SAEs that are attributed to a study procedure performed during the screening period (from the time of consent until the time of first dose of study drug).

The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study drug. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE. Beyond the reporting period, any unsolicited SAE assessed as related to IMGN632 by the Investigator will be processed and reviewed by the Sponsor. SAEs will be followed by the Sponsor's Pharmacovigilance team until resolution, stabilization, or return to baseline, regardless of study status or time since last IMGN632 administration.

The SAE form must be completed and submitted to the Sponsor (or CRO) within 24 hours of the Investigator's learning of the event. The report is sent to the contact printed on the SAE form and listed in the Study Manual and/or SAE completion instructions. All SAE reports must be maintained as part of the Investigator study files. Any follow-up information or query response must be submitted using the same time frames and to the same contacts using a follow-up SAE Report.

When reporting SAEs, the following additional points should be noted:

- For AESI (ie, infusion-related reactions; Section 10.4.2), complete the SAE form narrative, stating that the event is an AESI. If nonserious, leave seriousness criteria blank.

- The underlying diagnosis or syndrome should be reported as the primary SAE term, rather than the signs or symptoms (signs and symptoms may be described in the narrative).
- Progression of disease should not be reported as an SAE term; any serious medical event/condition that results from progression of underlying disease, if untoward, should be reported as the SAE. The applicable protocol eCRF page(s) pertaining to death should be appropriately completed however, as disease progression.
- Death should not be reported as an SAE term. Death is an outcome of a specific SAE term. In exceptional cases, "death of unknown cause" may be used as an event term until the cause of death has been determined. If an autopsy was performed, the autopsy report should be provided.
- For the purposes of expedited reporting, an SAE is classified by the Sponsor as unexpected when the nature or severity of the event is inconsistent with the information in the Investigator's Brochure for IMGN632.

10.8. Sponsor's Responsibility to Inform

It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of all Investigational New Drug (IND) Safety Reports (CIOMS/MedWatch) that have been submitted to the applicable regulatory agencies as notification of a suspected unexpected serious adverse reaction (SUSAR). These reports, summarizing the findings, serve to notify the Investigator of a potential safety signal as she/he fulfills the responsibilities of overseeing patient safety.

The Sponsor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication through annual updates to the Investigator's Brochure.

According to the FDA Guidance, Safety Reporting Requirements for IND and Bioavailability/Bioequivalence Studies, Dec 2012: "…a report that meets the criteria for reporting in an IND safety report should also be considered an "unanticipated problem" and reported to the IRB by the Investigator".

The Investigator (or Sponsor or Sponsor's representative if so designated) must promptly report all SUSARs to the IRB/IEC for review in accordance with global and local requirements, including reporting to Eudravigilance database in accordance with EU Clinical Trial Regulation. A copy of the CIOMS/MedWatch report and notification to IRB/IEC should be retained in the site's study files.

10.9. Reporting Pregnancy

Pregnancy and lactation are exclusion criteria in protocol IMGN632-0801. A WCBP, defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months), must agree to use effective contraceptive methods while on study treatment and for at least 7 months after the last dose of study drug as outlined in Section 5.3.

Patients who become pregnant during the study should be discontinued from the study drug immediately.

Although pregnancy itself is not considered an AE, all pregnancies occurring inadvertently during the study (pretreatment, treatment, and post-treatment period) must be reported immediately to the Sponsor (or CRO). Pregnancy is not recorded on the AE page of the eCRF but on the study-specific pregnancy report form.

In addition, any pregnancy or outcome of pregnancy brought to the attention of the Investigator after the study, and where it is known that study drug was taken at the time of conception, must also be reported to the Sponsor (or CRO) promptly.

With consent, pregnancy will be followed through delivery or final outcome for female patients who become pregnant and for female partners of male patients who become pregnant. The pregnancy report form is composed of 2 parts: the first part is used to collect information before the outcome of the pregnancy is known (eg, mother's details, obstetric history, and exposure to drugs during the current pregnancy). This should be completed as soon as possible after it has been identified that the patient received an investigation product during pregnancy and immediately sent to the Sponsor (or CRO). The second part of the form is used to record the outcome of the pregnancy. Both normal and adverse outcomes must be reported to the Sponsor (or CRO) within the timeframes specified for SAE. In the case of an adverse outcome of pregnancy, such as a congenital anomaly, a birth defect, or fetal death, a Parent-Child/Fetus report must also be completed, the event(s) assessed, and the report sent within the same timelines as for SAE.

11. STATISTICS

All descriptive statistical analyses will be performed using SAS software (version 9.4 or later), unless otherwise noted in the SAP. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the number of nonmissing values (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a detailed description of patient disposition; patient demographics and baseline characteristics will be summarized. PK data will be presented descriptively and graphically.

[redacted]

No formal interim analysis is planned for all other cohorts. However, a review of safety data and available preliminary PK data will be conducted by the CRC for each schedule at the following timepoints: once the last patient in a given cohort has completed the first cycle of treatment, the time at which a DLT is observed in at least 1 patient, and approximately every 2 weeks thereafter to monitor for the occurrence of DLT in all patients. During the Dose Expansion Phase of the trial, the CRC will monitor the occurrence of DLTs at least every 4 weeks.

The SAP will fully describe the planned analyses for this study and will be written after the final protocol and annotated CRFs are finalized and before the database lock.

11.1. Sample Size

Overall, approximately 208 patients will be enrolled in the study, allowing for dropouts and enlargement of dose escalation and dose expansion cohorts as needed.

11.1.1. Dose Escalation Phase

During the Dose Escalation Phase, ascending doses of IMGN632 were evaluated to identify the MTD in each schedule using a traditional 3 + 3 design. A total of 65 patients were treated during the Dose Escalation Phase.

After data review and selection of the recommended dose(s) and schedule(s), the Dose Expansion Phase of the study was opened.

11.1.2. Dose Expansion Phase

Patients enrolled in the Dose Expansion Phase will be assigned to 1 of 6 cohorts. The Dose Expansion Phase of the trial will accrue up to 190 patients, which includes up to 20 additional patients if a different dose level or schedule than Dose Expansion Cohort 2 needs to be investigated (Dose Expansion Cohort 5).

[redacted]

For Cohorts 2 through 5, 20-patient expansion cohorts were selected to allow measurement of a target CR rate of 60% while having a 90% CI to exclude a low response rate of 30%. If the observed CR rate is 12/20 (60%), then the 90% CI for CR rate will be 39% to 78%. Assuming the true CR rate is 60%, then the probability of observing at least 9 complete responders (out of 20) is 94%.

[redacted]

[redacted]

11.2. Pharmacokinetic Analyses

Pharmacokinetic parameters such as C_{max}, the time of maximal concentration (T_{max}), AUC from time 0 to the final observed concentration (AUC_{last}); the AUC extrapolated to infinite time (AUC_{∞}), the terminal half-life ($t_{1/2}$), volume of distribution, and clearance will be calculated as appropriate from concentration data with IMGN632, total antibody, and FGN849 using the actual sampling times when possible. Noncompartmental methods will be used to calculate PK parameters. Concentration data and PK parameters will be summarized descriptively by dose. Concentration time profiles will be presented graphically by dose level.

11.3. Safety Analyses

Adverse events and concomitant medication will be listed and summarized.

Adverse events will also be coded with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized per system organ class and preferred term.

Concomitant medications will be coded using the World Health Organization Drug Dictionary. A dictionary listing of all unique concomitant medications used in the study will be provided.

All hematology, blood chemistry, vital signs, and ECG results will be listed per patient for each assessment. Shifts in hematology and blood chemistry values from Baseline will be summarized.

11.4. Analysis of Antileukemia Activity

Overall response rate (ORR) is defined as the proportion of patients with the best overall response, as follows:

- AML, ALL, and other hematologic malignancies: CR_{MRD-}, CR, CRh, CRi, MLFS, or PR
- [redacted]

Composite complete remission (CCR) is defined as complete response as below:

- AML, ALL, and other hematologic malignancies: CR_{MRD-}, CR, CRh, or CRi
- [redacted]

ORR and CCR rate will be provided. The exact 95% CI for the ORR and CCR rates will be calculated using the method of Clopper-Pearson. Similar analyses will be carried out for the rates of the following responses:

- CR_{MRD-}/CR for AML, ALL, and other hematologic malignancies
- [redacted]

Changes in bone marrow blasts and treatment outcomes (shown below) will be calculated, summarized, and presented in tables and listings. Treatment outcomes will be calculated at 6 and 12 months and presented as rates if applicable.

Overall survival (OS) will be defined for all patients in the trial and will be measured from the date of first dose until death from any cause. For a patient who is not known to have died by the end of study follow-up, observation of OS will be censored on the date he or she was last known to be alive. The product limit method of Kaplan-Meier will be used to estimate survival probabilities.

Duration of CCR (DOCR) will be summarized using the Kaplan-Meier method in patients who had a CR or CRc. DOCR will be defined from the first response to the time of relapse or death from any cause, whichever comes first; for patients who did not relapse or die, the DOCR will be censored at the time of the last response assessment.

Similar analyses will be carried out for the durations of the following responses:

- [redacted]
- CR_{MRD-}/CR for AML, ALL, and other hematologic malignancies
- Best overall response

[redacted]

11.5. Quality Control and Assurance

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. Data will be captured using validated systems. Adverse events will be coded using the latest version of MedDRA. Concomitant medications will be coded using the World Health Organization Drug Dictionary (September 2015 or later version). Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals (eg, Laboratory Manuals and Pharmacy Manuals) will be provided to aid consistency in data collection and reporting across sites.

All required data will be entered into the clinical and/or safety database in accordance with Code of Federal Regulations 21 Part 11 compliance. The database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be given restricted access based on their role in the study through a password-protected environment. All missing data will be explained.

Data entered in the system must be verifiable against source documents and will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor, or its designee. If necessary, the study site will be contacted for corrections or clarifications.

The Sponsor will ensure that the clinical trial is conducted with a quality management system in order to ensure human subject protection and reliability of study results. Data will be generated,

documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements, including EU Clinical Trial Regulation.

12. ADMINISTRATIVE CONSIDERATIONS, STUDY MONITORING, AND DATA MANAGEMENT

12.1. Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed FDA Form 1572 or equivalent. Study drug may be administered only under the supervision of trained Investigators listed on this form. Curriculum vitae must be provided for the Investigators and Sub-Investigators listed on FDA Form 1572 or equivalent.

The Investigator should ensure that all persons assisting with the study are adequately informed and trained about the protocol, any amendments to the protocol, the study drug(s), and their study-related duties and functions prior to participation in the study. The Investigator must maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH GCP, and applicable local regulatory requirement(s), including EU Clinical Trial Regulation.

12.2. Ethical Conduct of the Study

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC approval of the protocol and the study ICF. This approval must refer to the ICF(s) and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year or as per institutional guidelines. The IRB/IEC must be notified of completion of the study and a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor or designee. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs that are subject to expedited reporting to the FDA or other regulatory agencies (SUSARs), must be submitted promptly to the IRB/IEC.

The study will be conducted in accordance with the protocol, Operations Manual, ICH guidelines, EU Clinical Trial Regulation, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.3. Patient Information and Consent

Before enrolling in the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form

understandable to him or her. An ICF that includes information about the study will be prepared and given to the patient. This document will contain all FDA- and ICH-required elements. The ICF must be in a language understandable to the patient and must specify who informed the patient.

After reading the informed consent document, the patient must give consent in writing. If the patient is unable to read, oral presentation and explanation of the written ICF and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the patient. The original signed and dated consent document will be retained by the Investigator. Patient confidentiality will be maintained as outlined in Section 12.4.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

If an amendment substantially alters the trial design, increases the potential risk to the patients, affects the treatment of the patient, or might otherwise influence the willingness of the patient to participate in the trial, then the ICF must be revised and submitted to the relevant IRB/IEC and, where necessary, to the relevant competent authorities, for review and approval. When a patient is currently undergoing trial procedures and is affected by the amendment, then the patient must be asked to consent again using the new ICF.

A model of the ICF to be used in this study will be provided to the sites separately from this protocol.

12.4. Patient Confidentiality

Patient names will not be supplied to the Sponsor. If the patient's name appears on any documents, it must be obliterated before a copy of the document is supplied to the Sponsor or designee (CRO). Study findings stored on a computer will be stored in accordance with local data protection laws. Patient scans, blood, and tissue samples sent to outside laboratories and/or CROs (eg, tissue analysis laboratory) are identified by study patient number only to ensure maintenance of confidentiality. The patient ICF will state that publications resulting from this study will not refer to patient name or include any other information that might disclose the identity of the patient. The patients will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Before patient data are shared with the Sponsor, the study investigator and staff will replace the patient's name, address, and contact information with a generic code which the Sponsor cannot link to that patient's identity to protect the confidentiality of the data.

For the personal data that the Sponsor of the submitted study controls and maintains, the Sponsor has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based Sponsor Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per the Sponsor's Information Security policies taking into account the sensitivity of the data.

The Sponsor has a data protection impact assessment program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect privacy of clinical trial subjects. The Sponsor also maintains robust security incident response policies and procedures, including requirements for the containment of any data-related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

The Sponsor shall document any personal data breaches for which it is a controller and notify where required the competent national supervisory authority without undue delay and at the latest within 72 hours after becoming aware of such an incident. The Sponsor shall create and maintain appropriate records of such an incident.

12.5. Study Monitoring

Monitoring procedures that comply with current GCP guidelines will be followed. On-site review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. On-site monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (eg, letter, telephone, email, and facsimile).

12.6. Case Report Forms and Study Reports

eCRFs are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original CRF entry must indicate the reason for the change. The Investigator is required to sign/e-sign the CRF after all data have been captured for each patient. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by re-signing the CRF.

12.7. Protocol Deviations

The Investigator will conduct the study in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will be reviewed by the Sponsor and may require submission to the IRB/IEC as per institutional guidelines.

12.8. Protocol Amendments

Any change to the protocol will be recorded in a written amendment. The signed amendment will be attached to this protocol. Amendment to the protocol may require regulatory submissions (eg, IRB/IEC) in accordance with local regulations. If this study is a regulatory commitment, changes to the protocol will be implemented with approval from the applicable regulatory authorities. In some cases, an amendment may require a change to the ICF.

12.9. Start and Completion of the Study

The start of study is defined as the date of the first site activated.

The end of study will be defined as the latter of the completion of the Safety Follow-up visit for the last patient remaining on treatment or 2 years from the last accrued patient's first visit.

12.10. Study Termination

12.10.1. Study Termination

If the Sponsor, an Investigator, or Study Clinical Monitor discovers conditions arising during the study that indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study must be terminated after appropriate consultation between the Sponsor and the Investigators. In addition, a decision on the part of the Sponsor to suspend or discontinue development of the test material may be made at any time.

Within 15 days of premature closure, the Sponsor must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

12.10.2. Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site
- Failure of the Investigator to enter patients at an acceptable rate
- Insufficient adherence by the Investigator to protocol requirements
- Insufficient, incomplete, and/or unevaluable data

12.11. Source Documentation

Source data are defined as the original documents, data, and records. This includes but is not limited to the following: hospital records, clinic and office charts, study-specific source document worksheets, phone logs, laboratory requisitions and reports, images, local laboratory reports (if applicable), electronic data/information sources and any other documentation regarding the patients.

12.12. Sponsor Audits and Inspections by Regulatory Agencies

For the purpose of ensuring compliance with the clinical trial protocol, GCP and other applicable regulatory requirements, the Investigator shall permit auditing by or on behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection. The confidentiality of the data verified, and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

12.13. Retention of Records

The Investigator must maintain confidential study documentation and prevent accidental or premature destruction of those documents 2 years after a marketing application for the product has been approved. The Investigator is responsible for ensuring compliance with local regulatory retention requirements. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed-upon designee.

12.14. Publication and Disclosure Policy

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

Information obtained during the conduct of this study will be used by the Sponsor in connection with the development of IMGN632. The study Investigator is obliged to provide the Sponsor

with complete test results and all data developed in this study. The Sponsor has full ownership of the original CRFs completed as part of the study. This information may be disclosed to other physicians who are conducting similar studies and to the FDA as deemed necessary by the Sponsor. Patient-specific information may be provided to other appropriate medical personnel related to the care of that patient only with the patient's prior consent.

The Investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the Sponsor, provided the Sponsor a copy of the draft document intended for publication, and obtained the Sponsor's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential. The Sponsor will use the information for registration purposes and for the general development of the drug.

12.14.1. For EU Clinical Trials Regulation Submissions Publication Policy

The Sponsor is committed to fostering the highest standard of conduct related to Scientific Publications and transparency, while at the same time, protecting its confidential information. Authorship related to scientific publications shall be determined in accordance with and governed by the criteria defined by the International Committee of Medical Journal Editors "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals." It is required that the Sponsor's role in support of the study be appropriately disclosed in any Institution or scientific publications.

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APPENDIX A. SCHEDULE OF ASSESSMENTS – SCHEDULE A

Activity	Screening		Cycles 1 and 2					Cycles ≥ 3[a]			End of Treatment	30-Day Follow-Up	12-Week Response Follow-Up[b]
Day(s)	-28 to -1	-14 to -1	1	2	3	8	15	1	8	15			
Visit window				+ 1	+ 1	± 1	± 2	+ 2	± 1	± 2		+ 14	± 3 Weeks
Informed consent	●												
Demography	●												
Medical history	●												
Confirm disease diagnosis	●												
Record baseline signs and symptoms		●	●										
Review and document I/E criteria		●											
Confirm patient continues to satisfy I/E criteria (Section 4.1/Section 4.2)			●										
Confirm patient meets retreatment criteria (Section 5.1.1/Section 5.1.3)			●					●					
Height	●												
Complete physical examination		●										●	
Symptom-directed physical examination			●	●		●	●	●	●	●	●		
Weight		●	●			●	●	●	●	●		●	
Vital signs (BP, heart rate, RR, T)[c]		●	●			●	●	●	●	●	●	●	
Observe for infusion-related reactions[c]			●										
LVEF assessment (ECHO or other)	●												
ECOG		●	●					●			●	●	
Hematology		●	●[d]			●[d]	●	●	●	●	●	●	●
Serum chemistry		●	●[e]			●	●	●	●	●	●	●	

Activity	Screening		Cycles 1 and 2					Cycles ≥ 3[a]			End of Treatment	30-Day Follow-Up	12-Week Response Follow-Up[b]
Day(s)	**-28 to -1**	**-14 to -1**	**1**	**2**	**3**	**8**	**15**	**1**	**8**	**15**			
Visit window				**+ 1**	**+ 1**	**± 1**	**± 2**	**+ 2**	**± 1**	**± 2**		**+ 14**	**± 3 Weeks**
Coagulation (PT/INR/aPTT)		●[d]										●	
Urinalysis		●	●[d]					●				●	
Pregnancy test (urine or serum)[f]		●						●[f]				●	
Bone marrow aspirate[g]	●		●[g]					●[g]				●[h]	●
CT/PET imaging – BPDCN patients only	[redacted]												
Skin assessment – BPDCN patients only													
Subsequent anticancer treatment information											●	●	
12-lead ECG[k]		●	●	●	●			●			●		
IMGN632 infusion			●					●					
AE assessments	●[l]												
Record concomitant medications		●											

AE = adverse event; aPTT = activated partial thromboplastin time, BMA = bone marrow aspirate, BP = blood pressure, BPDCN = blastic plasmacytoid dendritic cell neoplasm, CT/PET = computed tomography/positron emission tomography, ECG = electrocardiogram, ECHO = echocardiogram, ECOG = Eastern Cooperative Oncology Group, I/E = inclusion/exclusion, INR = international normalized ratio, LVEF = left ventricular ejection fraction, PD = progressive disease, PT = prothrombin time, RR = respiratory rate, SAE = serious adverse event, T = temperature, WCBP = women of child bearing potential.

[a] In Cycle 4 and beyond, the Day 8 and Day 15 visits are considered optional, based on the clinical status of the patient per the assessment of the Investigator.

[b] Patients who discontinue for reasons other than PD should undergo disease assessments (Section 9.15.1) every 12 weeks (± 3 weeks) until documentation of PD, the initiation of a subsequent anticancer therapy, or 2 years from the time of study drug discontinuation, whichever comes first. After documentation of PD or initiation of new anticancer therapy, the patient should be contacted every 12 weeks (± 3 weeks) for the subsequent use of anticancer therapy as well as survival until 2 years from patient's last dose of study drug.

[c] To monitor for potential infusion-related reactions, it is recommended that vital signs be assessed within 30 minutes before dose and approximately every 15 minutes (or as indicated by institutional practice) for at least 1 hour following infusion. For the first infusion of IMGN632, additional assessments will be performed approximately every 30 minutes for at least 4 hours, or longer as clinically indicated.

[d] Day 1 laboratory assessments may be performed up to 3 days prior to study drug administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN632. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 3 days of dosing and are within acceptable ranges.

Erythrocyte sedimentation rate (or equivalent) and von Willebrand factor to be assessed prior to each IMGN632 dose (Day 1) and 7 days post dose (Day 8) of each cycle if these tests are available. For a complete list of laboratory assessments, refer to Section 9.13.

[e] Day 1 laboratory assessments may be performed up to 3 days before study drug administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN632. In the event of severe nonhematologic toxicity, repeat laboratory tests should be performed as necessary until the toxicity resolves or stabilizes. For a complete list of laboratory assessments, refer to Section 9.13. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 3 days of dosing and are within acceptable ranges.

[f] For WCBP, a serum pregnancy test will be performed at screening prior to enrollment (not more than 3 days before the first dose of IMGN632), and a urine or serum test will be performed at every other cycle while on study and at the 30-Day Follow-up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.

[g] BMA is to be done during the Screening period or on Cycle 1, Day 1 prior to first dose. Existing bone marrow results may be used if within the 28-day screening window. BMA may be performed any time within ± 1 week of Cycle 2, Day 1. In subsequent cycles, BMA may be performed as clinically indicated.

[h] As clinically indicated

[redacted]

[k] Pre-dose ECGs are to be conducted on Day 1 of every cycle, and post-dose ECGs are conducted in Cycle 1 ONLY; ECGs will be performed as outlined in Section 9.8. Refer to Appendix D for information on time-matched PK sampling.

[l] Only AEs attributed to study procedures are recorded at baseline. All SAEs and those AEs assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first.

APPENDIX B. SCHEDULE OF ASSESSMENTS – SCHEDULE B

Activity	Screening		Cycles 1 and 2							Cycles ≥ 3[a]				End of Treatment	30-Day Follow-Up
Day(s)	-28 to -1	-14 to -1	1	2	4	8	9	10	15	1	4	8	15		
Visit window				+1	+1	+1	+1	+1	±2	+2	+1	±1	±2		+14
Informed consent	●														
Demography	●														
Medical history	●														
Confirm disease diagnosis	●														
Record baseline signs and symptoms		●	●												
Review and document I/E criteria		●													
Confirm patient continues to satisfy I/E criteria (Section 4.1/Section 4.2)			●												
Confirm patient meets retreatment criteria (Section 5.1.1/Section 5.1.3)			●							●					
Height	●														
Complete physical examination		●													●
Symptom-directed physical examination			●	●	●	●	●		●	●	●	●	●	●	
Weight		●	●		●	●			●	●	●	●	●		●
Vital signs (BP, heart rate, RR, T)[b]		●	●		●	●			●	●	●	●	●	●	●
Observe for infusion-related reactions[b]								●							
LVEF assessment (ECHO or other)	●														
ECOG		●	●							●				●	●
Hematology		●	●[c]		●	●[c]			●	●	●	●	●	●	●
Serum chemistry		●	●[d]			●			●	●		●	●	●	●
Coagulation (PT/INR/aPTT)		●[c]													●

Activity	Screening		Cycles 1 and 2							Cycles ≥ 3[a]				End of Treatment	30-Day Follow-Up
Day(s)	-28 to -1	-14 to -1	1	2	4	8	9	10	15	1	4	8	15		
Visit window				+1	+1	+1	+1	+1	±2	+2	+1	±1	±2		+14
Urinalysis		●	●[c]							●					●
Pregnancy test (urine or serum)[e]		●								●[e]					●
Bone marrow aspirate[f]	●		●[f]							●[f]					●[g]
CT/PET imaging – BPDCN patients only	[redacted]														
Skin assessment – BPDCN patients only															
Subsequent anticancer treatment information														●	●
12-lead ECG[j]		●	●			●	●	●		●				●	
IMGN632 infusion			●		●	●				●	●	●			
AE assessments	●[k]														
Record concomitant medications		●													

AE = adverse event; aPTT = activated partial thromboplastin time; BMA = bone marrow aspirate; BP = blood pressure; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CT/PET = computed tomography/positron emission tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; I/E = inclusion/exclusion; INR = international normalized ratio; LVEF = left ventricular ejection fraction; PT = prothrombin time; RR = respiratory rate; SAE = serious adverse event; T = temperature; WCBP = women of childbearing potential.

[a] In Cycle 4 and beyond, Days 8 and 15 visits are considered optional, based on the clinical status of the patient per the assessment of the Investigator.

[b] To monitor for potential infusion-related reactions, vital signs are recommended to be assessed within 30 minutes prior to dose and approximately every 15 minutes (or as indicated by institutional practice) for at least 1 hour following infusion. For the first infusion of IMGN632, additional assessments will be performed approximately every 30 minutes for at least 4 hours, or longer as clinically indicated.

[c] Day 1 laboratory assessments may be performed up to 3 days prior to study drug administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN632. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 3 days of dosing and are within acceptable ranges. Erythrocyte sedimentation rate (or equivalent) and von Willebrand factor to be performed prior to each IMGN632 dose (Day 1) and 7 days post dose (Day 8) of each cycle if these tests are available. For a complete list of laboratory assessments, refer to Section 9.13.

[d] Day 1 laboratory assessments may be performed up to 3 days prior to study drug administration. Laboratory results must be reviewed prior to each scheduled administration of IMGN632. In the event of severe nonhematologic toxicity, repeat laboratory tests should be performed as necessary until the toxicity resolves

or stabilizes. For a complete list of laboratory assessments, refer to Section 9.13. Repeat testing on Cycle 1, Day 1 is not required if tests were obtained within 3 days of dosing and are within acceptable ranges.

[e] For WCBP, a serum pregnancy test will be performed at screening prior to enrollment (not more than 3 days before the first dose of IMGN632), and a urine or serum test will be performed at every other cycle while on study and at the 30-Day Follow-up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.

[f] BMA is to be done during the Screening period or on Cycle 1, Day 1 prior to first dose. Existing bone marrow results may be used if within the 28-day screening window. BMA may be performed any time within ± 1 week of Cycle 2, Day 1. In subsequent cycles, BMA may be performed as clinically indicated.

[g] As clinically indicated

[redacted]

[j] Pre-dose ECGs are to be conducted on Day 1 and Day 8 of Cycle 1; post-dose ECGs are conducted in Cycle 1 ONLY (end of Cycle 1, Day 8 infusion within 30 minutes from PK blood draw; 24 ± 2 hours [Day 9] and 48 ± 2 hours [Day 10] post Day 8 infusion). In subsequent cycles, a single ECG will be performed pre-dose on Day 1 only. ECGs will be performed as outlined in Section 9.8. Refer to Appendix E for information on time-matched PK sampling.

[k] Only AEs attributed to study procedures are recorded at baseline. All SAEs and those AEs assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first.

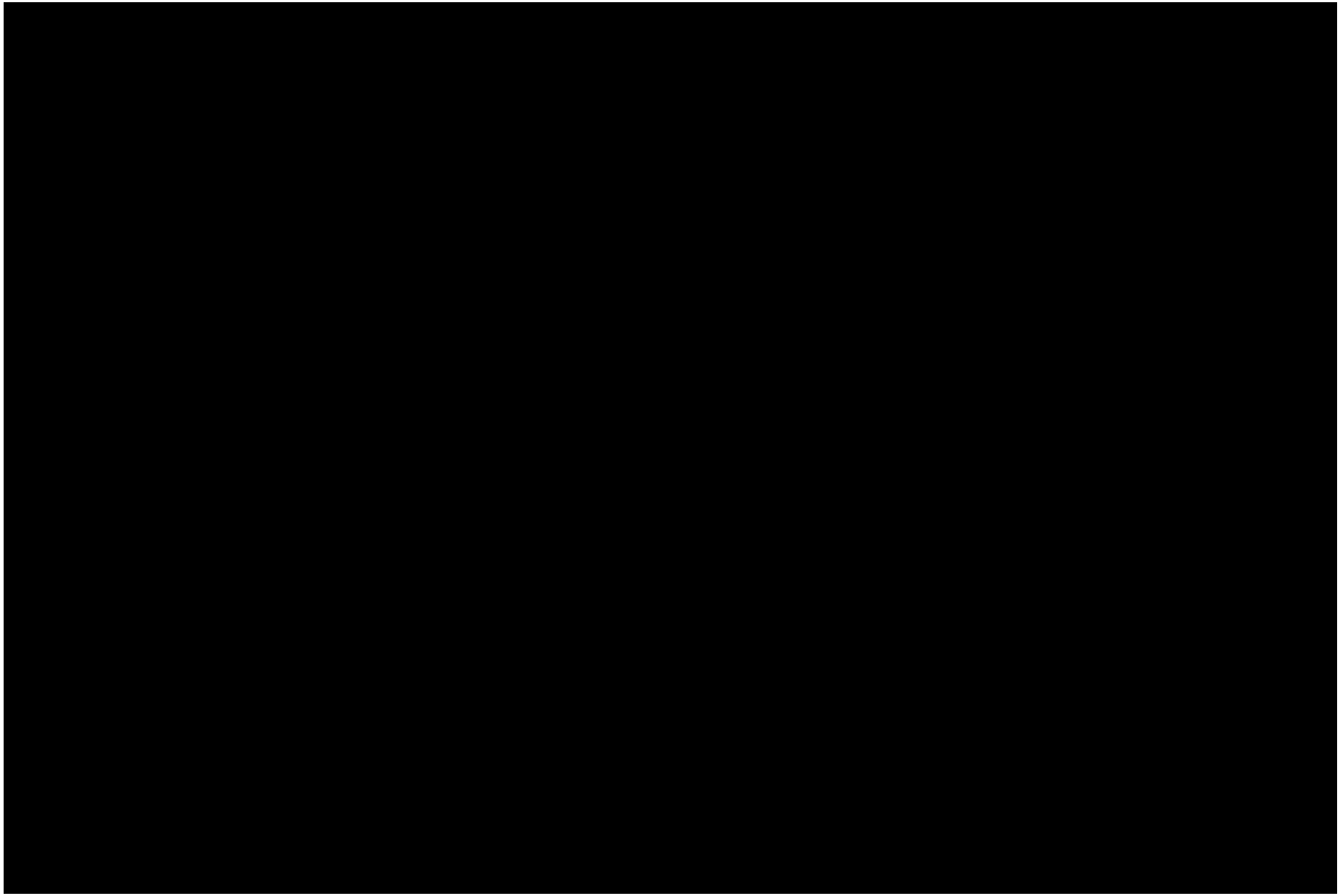
APPENDIX C. SCHEDULE OF ASSESSMENTS – BPDCN EXPANSION (SCHEDULE A)

Activity	Screening	Cycles 1 and 2	Cycles ≥ 3[a]	End of Treatment	30-Day Follow-Up[b]	12-Week Response Follow-Up[c]
Day(s)	[redacted]					
Visit window						
Informed consent						
Demography						
Medical history						
Record signs and symptoms						
Review and document I/E criteria						
Confirm patient continues to satisfy I/E criteria (Section 4.1/Section 4.2)						
Confirm patient meets retreatment criteria (Section 5.1.1/Section 5.1.3)						
Lumbar puncture[e]						
Complete physical examination						
Symptom-directed physical examination						
Weight						
Vital signs (BP, heart rate, RR, T)[f]						
Observe for infusion-related reactions[f]						
LVEF assessment (ECHO or other)						

Activity	Screening	Cycles 1 and 2	Cycles ≥ 3[a]	End of Treatment	30-Day Follow-Up[b]	12-Week Response Follow-Up[c]
Day(s)	[redacted]					
Visit window						
ECOG						
Hematology/serum chemistry						
Coagulation (PT/INR/aPTT)						
Urinalysis						
Pregnancy test (urine or serum)[i]						
Bone marrow aspirate[j]						
CT/PET imaging[l]						
Skin assessment – biopsy skin lesions[m]						
Subsequent anticancer treatment information						
12-lead ECG[n]						
IMGN632 infusion						
AE assessments	●[o]					
Record concomitant medications		●				

AE = adverse event; aPTT = activated partial thromboplastin time; BMA = bone marrow aspirate; BP = blood pressure; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CNS = central nervous system; CT/PET = computed tomography/positron emission tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; I/E = inclusion/exclusion; INR = international normalized ratio; LVEF = left ventricular ejection fraction; mSWAT = Modified Severity-Weighted Assessment Tool; PD = progressive disease; PT = prothrombin time; RR = respiratory rate; SAE = serious adverse event; T = temperature; WCBP = women of childbearing potential.

[a] In Cycle 4 and beyond, Days 8 and 15 visits are considered optional, based on the clinical status of the patient per the assessment of the Investigator.



[redacted]

º Only AEs attributed to study procedures are recorded at baseline. All SAEs and those AEs assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first.

APPENDIX D. PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS – SCHEDULE A

Activity	Screening	Cycles 1 and 3					Cycles 2 and 4-6	EOT	30-Day FU
		Day 1	Day 2	Day 3	Day 8	Day 15	Day 1		
[redacted]									
Blood sample for PK assessments		●[e]	●[e]	●[e]	●[e]	●[e]	●[f]	●	●
[redacted]									

ADA = antidrug antibody; BMA = bone marrow aspirate; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete remission; CRc = complete remission with minimal residual skin abnormality; CRh = complete remission with partial hematologic recovery; CRi = complete remission/response with incomplete recovery; CR_{MRD-} = complete remission without minimal residual disease; EOT = End of Treatment; FcγR = fragment crystallizable gamma receptor; FU = Follow-up; MLFS = morphologic leukemia-free state; Pd = pharmacodynamic; PK = pharmacokinetic; PR = partial response.
Note: if possible, blood transfusions should be avoided on the same day of IMGN632 dosing and be delayed to the following day [redacted]

[e] PK, Cycles 1 and 3: samples to be taken pre-dose and at the end of the IMGN632 infusion (+ 10 minutes), at 2 hours (± 10 minutes), 4 hours (± 15 minutes), and 6 hours (± 1 hour), 24 hours (± 4 hours), 48 hours (± 6 hours), 168 hours (± 24 hours), 336 hours (± 24 hours) after the completion of the IMGN632 infusion.

[f] PK, Cycles 2 and 4-6, Day 1: samples to be taken pre-dose and at the end of the IMGN632 infusion (+ 10 minutes) [redacted]

APPENDIX E. PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS – SCHEDULE B

Activity	Screening	Cycles 1 and 3						Cycles 2 and 4-6			EOT	30-Day FU
		Day 1	Day 4	Day 8	Day 9	Day 10	Day 15	Day 1	Day 4	Day 8		
[redacted]												
Blood sample for PK assessments		•[f]	•[f]	•[f]	•[f]	•[f]	•[f]	•[g]	•[g]	•[g]	•	•
[redacted]												

ADA = antidrug antibody; BMA = bone marrow aspirate; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete remission; CRc = complete remission with minimal residual skin abnormality; CRC = cohort review committee; CRh = complete remission with partial hematologic recovery; CRi = complete remission/response with incomplete recovery; CR_{MRD-} = complete remission without minimal residual disease; EOT = End of Treatment; FcγR = fragment crystallizable gamma receptor; MLFS = morphologic leukemia-free state; Pd = pharmacodynamic; PK = pharmacokinetic; PR = partial response.
Note: if possible, blood transfusions should be avoided on the same day of IMGN632 dosing and be delayed to the following day.

[redacted]

[f] PK, Cycles 1 and 3: samples to be taken pre-dose and at the end of the IMGN632 infusion (+ 10 minutes) on Day 1; pre-dose and at the end of the second IMGN632 infusion (+ 10 minutes) on Day 4 (if applicable, based on the decision of the CRC prior to opening Schedule B); pre-dose and at the end of the Day 8 infusion (+ 10 minutes) and at 2 hours (± 10 minutes), 4 hours (± 15 minutes), 6 hours (± 1 hour), 24 hours (± 4 hours), 48 hours (± 6 hours), and 168 hours (± 24 hours) after the completion of the Day 8 infusion.

[g] PK, Cycle 2, and Cycles 4-6: samples to be taken pre-dose and at the end of the IMGN632 infusion (+ 10 minutes) on Day 1, Day 4, and Day 8.

[redacted]

APPENDIX F. PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS – BPDCN EXPANSION

Activity	Screening	Cycles 1 and 3				Cycles 2 and 4	Cycles ≥ 5	EOT	30-Day FU
		Day 1	Day 2	Day 3	Day 8	Day 1	Day 1		
[redacted]									
Blood sample for PK assessments		●[b]	●[b]	●[b]	●[b]	●[c]		●	●
[redacted]									

ADA = antidrug antibody; BMA = bone marrow aspirate, BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete remission; CRc = complete remission with minimal residual skin abnormality; CRh = complete remission with partial hematologic recovery; CRi = complete remission/response with incomplete recovery; EOT = End of Treatment; FcγR = fragment crystallizable gamma receptor; FU = Follow-up; PK = pharmacokinetic; PR = partial response.
Note: if possible, blood transfusions should be avoided on the same day of IMGN632 dosing and be delayed to the following day.
[redacted]

[b] PK, Cycles 1 and 3: samples to be taken pre-dose and at the end of the IMGN632 infusion (+ 10 minutes), at 2 hours (± 10 minutes), 4 hours (± 15 minutes), and 6 hours (± 1 hour), 24 hours (± 4 hours), 48 hours (± 6 hours), and 168 hours (± 24 hours) after the completion of the IMGN632 infusion.

[c] PK, Cycles 2 and 4, Day 1: samples to be taken pre-dose and at the end of the IMGN632 infusion (+ 10 minutes).

[redacted]

APPENDIX G. RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA AND OTHER HEMATOLOGIC MALIGNANCIES EXCEPT BPDCN

(Modified International Working Group criteria (Cheson 2003), 2017 European LeukemiaNet Response Criteria (Döhner 2017), and CRh from the IDHIFA® (enasidenib) prescribing information)

1. CR without minimal residual disease (CR_{MRD-}):
    a. CR with negativity for a genetic marker by reverse transcription quantitative polymerase chain reaction (RT-qPCR), or CR with negativity by multiparameter flow cytometric (MFC)
2. Complete remission (CR): all of the following:
    a. Morphologic CR < 5% blasts
    b. Absolute neutrophil count (ANC) > 1000/µL
    c. Platelets ≥ 100,000/µL
    d. Patient independent of transfusions
    e. No residual evidence of active extramedullary disease
    f. MRD+ or unknown
3. Complete remission with partial hematologic recovery (CRh):
    a. Meets requirements for CR except ANC > 500/µL AND platelets > 50,000/µL
4. Complete remission/response with incomplete recovery (CRi):
    a. Meets requirements for CR except either ANC < 1000/µL or platelets < 100,000/µL.
5. Morphologic leukemia-free state (MLFS):
    a. Bone marrow < 5% blasts in an aspirate with spicules
    b. No blasts with Auer rods or persistence of extramedullary disease
    c. Marrow should not merely be “aplastic”; at least 200 cells should be enumerated or cellularity should be at least 10%
6. Partial response (PR):
    a. Decrease of at least 50% in the percentage of blasts to 5% to 25% in the BMA and the normalization of blood counts, as noted above
7. Relapse following complete response is defined as reappearance of leukemia blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (eg, bone marrow regeneration after consolidation therapy [or extramedullary relapse]).
8. Stable disease (SD):
    a. Absence of CR_{MRD-}, CR, CRh, CRi, PR, MLFS; and criteria for PD not met

9. Progressive disease (PD):
    a. Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:
        i. Increased or persistent bone marrow disease without at least a 100% improvement (ie, a doubling) in ANC to an absolute level (> 0.5×10^9/L [500/μL], and/or platelet count to > 50×10^9/L [50,000/μL] nontransfused):
            1. > 50% increase in bone marrow blasts over baseline (a minimum 15 percentage point increase is required in cases with < 30% blasts at baseline); or
            2. Persistent bone marrow blast percentage of > 70% over at least 3 months
        ii. > 50% increase in peripheral blasts (white blood cell count × % blasts) to > 25×10^9/L (> 25,000/μL) (in the absence of differentiation syndrome); or
        iii. New extramedullary disease.

Other response assessments (optional, performed by the local sites at the Investigator's discretion):

1. MRD testing by flow cytometry or PCR may be performed at local sites and reported on this study.
2. Cytogenetic response testing may be performed at local sites and reported on this study
3. Molecular response testing of genetic lesions (mutations/translocations) may be performed at local sites and reported on this study

APPENDIX H. RESPONSE CRITERIA FOR BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

As of Amendment 6.0, the assessment criteria used for BPDCN patients are as follows:

Response	Location	Criteria
Complete Response (CR)	Marrow	Normalization of blast percentage (≤ 5%)
	Peripheral Blood	Normalization of neutrophil count (≥ 1000/µL) and platelet count (≥ 100,000/µL) Absence of leukemic blasts
	Skin	100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline
	Nodal Masses	Regression to normal size on computed tomography (CT)
	Spleen, Liver	Not palpable, nodules disappeared
CR (clinical) with minimal residual skin abnormality (CRc)	Marrow	Normalization of blast percentage (≤ 5%)
	Peripheral Blood	Normalization of neutrophil count (≥ 1000/µL) and platelet count (≥ 100,000/µL) Absence of leukemic blasts
	Skin	Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)
	Nodal Masses	Regression to normal size on CT
	Spleen, Liver	Not palpable, nodules disappeared
CR (clinical) with partial hematologic recovery (CRh)	Marrow	Normalization of blast percentage (≤ 5%)
	Peripheral Blood	Normalization of neutrophil count (≥ 500/µL) AND platelet count (≥ 50,000/µL) Absence of leukemic blasts
	Skin	Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)
	Nodal Masses	Regression to normal size on CT
	Spleen, Liver	Not palpable, nodules disappeared
CR (clinical) with incomplete recovery (CRi)	Marrow	Normalization of blast percentage (≤ 5%)
	Peripheral Blood	Normalization of neutrophil count (≥ 1000/µL) OR platelet count (≥ 100,000/µL) Absence of leukemic blasts
	Skin	Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)
	Nodal Masses	Regression to normal size on CT
	Spleen, Liver	Not palpable, nodules disappeared

Response	Location	Criteria
Partial Response (PR)	Marrow	Decreased by > 50% in blast percentage to 5%-25%
	Skin	50% to < 100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline
	Nodal Masses	≥ 50% decrease in the sum of the product of the diameters (SPD) of up to 6 largest dominant masses; no increase in size of other nodes
	Spleen, Liver	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver of spleen
Stable Disease (SD)		Failure to achieve at least a PR, but no evidence of progression for at least 8 weeks
Relapse after CR/CRi/CRc	Marrow	Blast percentage > 5% (if no peripheral blasts, then confirmation aspirate required ≥ 1 week later)
	Peripheral Blood	Presence of leukemic blasts
	Skin	Increase in skin score greater than the sum of nadir plus 50% baseline score
	Nodal Masses	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase from nadir in SPD of more than 1 node, or ≥ 50% increase from nadir in longest diameter of a previously identified node > 1 cm in short axis
	Spleen, Liver	> 50% increase from nadir in the SPD of any previous lesions
Progressive Disease (PD)	Marrow	Any new lymph nodes or new skin lesions OR increase from nadir by > 50% of SPD of any single previously involved lymph node or total assessed lymph node masses OR >50% increase in bone marrow blast percentage
	Nodal Masses	
	Skin	

Hematologic parameters, ie, neutrophil and platelet counts, may be assessed up to 14 days following bone marrow assessment to make formal response criteria assessment.

APPENDIX I. MODIFIED SEVERITY-WEIGHTED ASSESSMENT TOOL (MSWAT) FOR BPDCN SKIN LESION ASSESSMENT

SITE NUMBER:_____

SUBJECT ID:_____ SUBJECT INITIALS:_____

ASSESSMENT DATE:_____ VISIT:_____

Body Region	**Approx. % Body Surface Area of Entire Body Region**	**% Body Surface Area Assessment of Involvement in Patient's Skin**		
		Patch*	**Plaque†**	**Tumor‡**
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion body surface area				
Weighting factor		× 1	× 2	× 4
Subtotal lesion body surface area × weighting factor				

Note: mSWAT score equals summation of each column line.
* Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
† Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
‡ Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.
Source: Olsen 2011.

MD Printed Name:_____ MD Signature:_____

APPENDIX J. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

Grade	Scale
0	Fully active, able to carry out all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

Source: Oken 1982

APPENDIX K. COMPUTED TOMOGRAPHY/POSITRON EMISSION TOMOGRAPHY SCANS

In this Phase 1/2 clinical trial, we are assessing response in BPDCN patients using formal response criteria, which includes assessment of CT/PET scans. As BPDCN is assessed as both a leukemia and as a solid tumor, we need the following information to be collected in the radiology reports from these scans:

Screening CT/PET scan:

General description of disease involvement and specific identification of up to 6 index lesions with 2 dimensions measured for each lesion, with individual standard uptake value measurements if available. Comment about the liver and spleen sizes and any involvement.

Subsequent CT/PET scans:

General description of disease involvement with specific comment if new lesions are present, specific comment about whether there is an **increase in size of the spleen and liver with dimensions**, and **specific comparison of the same screening lesions (up to 6 index lesions)** noting their **new 2 dimensions** (and change in standard update values if possible).

These index lesion measurements are used to calculate the **sum of the product of their diameters**, and this aggregate is used to calculate the percent change in lesions, which is essential for the determination of formal responses. This should be done as it is done for solid tumor response criteria (ie, Response Evaluation Criteria in Solid Tumours [RECIST]), but the levels of percent change are different in the response criteria.

https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

NOTE: May require additional efforts with radiologist. Please notify your department prior to initial PET scan.