A PHASE 1/2 DOSE-FINDING STUDY TO EVALUATE THE SAFETY, FEASIBILITY, AND ACTIVITY OF BPX-701, A CONTROLLABLE PRAME T-CELL RECEPTOR THERAPY, IN HLA-A2+ SUBJECTS WITH RELAPSED ACUTE MYELOID LEUKEMIA, PREVIOUSLY TREATED MYELODYSPLASTIC SYNDROME, OR METASTATIC UVEAL MELANOMA

Protocol Number:	**BP-011**
Investigational Products:	**BPX-701** – Autologous T cells genetically modified to express the αβ T cell receptor reacting with PRAME peptide/HLA-A2.01 (PRAME TCR) and an inducible caspase-9 (iCasp9) safety switch **Rimiducid –** dimerizer infusion to activate iCasp9 and induce apoptosis of the BPX-701 T cells in the event of toxicity
Study Sponsor:	**Bellicum Pharmaceuticals, Inc.** 2130 W. Holcombe Blvd, Suite 800 Houston, TX 77030
Medical Monitor Contact Information:	**Primary Medical Monitor:** [redacted] **Backup Medical Monitor:** [redacted]
ClinicalTrials.Gov Number:	**NCT02743611**
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INVESTIGATOR AGREEMENT SIGNATURE PAGE

I have read this protocol and agree to comply with all provisions set forth in this protocol, including all statements regarding confidentiality, and to complete the study within the time designated.

I assume responsibility for the conduct of this study at my study site. I will ensure that I have sufficient resources allocated to this project such that the safety of my subjects is protected at all times and that I complete my obligations to the sponsor according to the agreed timelines. I will delegate responsibilities only to those who are qualified by training and experience. I will ensure the integrity of the data generated by my team and that all team members are familiar with the study protocol and the study medication.

I agree that I will grant access to the applicable records, my staff allocated to the conduct of this protocol and my facilities for the purposes of monitoring, auditing and any required inspections associated with the conduct of this clinical trial.

I agree to comply with the ICH Guideline on Good Clinical Practice, applicable EMA regulations and applicable FDA guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

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Name
Investigator _____

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Protocol Number BP-011

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Protocol Title:

A phase 1/2 dose-finding study to evaluate the safety, feasibility, and activity of BPX-701, a controllable PRAME T-cell receptor therapy, in HLA-A2+ subjects with relapsed acute myeloid leukemia or myelodysplastic syndrome, or metastatic uveal melanoma

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PROTOCOL SYNOPSIS

Protocol No. :	BP-011
Protocol Title:	A Phase 1/2 Dose-Finding Study to evaluate the Safety, Feasibility, and Activity of BPX-701, a Controllable PRAME T-cell Receptor Therapy, in HLA-A2+ Subjects with Relapsed Acute Myeloid Leukemia, Previously Treated Myelodysplastic Syndrome, or Metastatic Uveal Melanoma
Study Phase:	Phase 1/2
Duration of Study:	**Subject Accrual:** Approximately 18-24 Months **Screening Period:** Up to 42 Days prior to BPX-701 T cell infusion **Treatment Period:** Up to 12 Months following BPX-701 T cell infusion **Posttreatment Follow Up Period:** Up to 15 Years following BPX-701 T cell infusion
Number of Subjects:	Up to 116 subjects
Number of Sites:	Up to 12
Study Design:	This is a Phase 1/2, multicenter, open-label, non-randomized study to characterize the feasibility, safety, and clinical activity of BPX-701, a genetically modified autologous T cell product incorporating an HLA-A2.01-restricted PRAME-directed T cell receptor (TCR) and an inducible caspase-9 (iCasp9) safety switch, when administered to subjects with relapsed acute myeloid leukemia (AML; Arm 1), previously treated myelodysplastic syndrome (MDS; Arm 1) or metastatic uveal melanoma (Arm 2). Arms 1 and 2 will be conducted in parallel. For each Arm, the study will be comprised of multiple parts, beginning initially with Part 1 (Phase 1). Treatment will be administered in an inpatient setting. Subject safety will be monitored throughout all parts of the study by a safety review team established by the sponsor. **Part 1 (or Phase 1) is a Cell Dose Escalation** phase to identify the recommended BPX-701 cell dose for expansion (RDE) using a 3+3 dose escalation design (escalating doses from 1.25 x 10^6 cells/kg up to 5.0 x 10^6 cells/kg administered by intravenous infusion). Dose escalation will proceed in sequential cohorts of at least 3 and up to 6 subjects until an RDE is defined. RDE is represented by the dose of BPX-701 that provides adequate T cell persistence and biological activity while not exceeding the

	maximum tolerated dose (MTD) or maximum administered dose. For the initial cell dose escalation cohort in each of Arms 1 and 2, the first 3 subjects will be enrolled sequentially with subjects 2 and 3 enrolled no sooner than 1 month (28 days) after the prior subject has been infused with BPX-701. All subsequent subjects will be enrolled in the usual manner for a 3+3 design. The evaluation period for defining dose limiting toxicity (DLT) and informing dose escalation decisions is from the start of the BPX-701 infusion on Day 0 through Day 28. DLT is defined as any of the following unless clearly due to disease progression or extraneous causes: • Any treatment-emergent CTCAE Grade 4 or 5 cytokine release syndrome (CRS) • Any treatment-emergent CTCAE Grade 3 CRS that does not resolve to Grade ≤2 within 7 days • Any treatment-emergent autoimmune toxicity Grade ≥3 • CTCAE Grade ≥3 infusion reaction • Any other treatment-emergent CTCAE Grade ≥3 organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing or due to the underlying malignancy that does not resolve to Grade ≤2 within 7 days **Parts 2 and 3 (Phase 2) comprise a Dose Expansion** phase to further assess safety, pharmacodynamics (including BPX-701 T cell persistence and response to rimiducid as applicable), and clinical activity of BPX-701 T cells administered at the RDE. Part 2 will begin once an RDE is determined in Part 1 (i.e., RDE-1 triggers Part 2 for Arm 1; RDE-2 triggers Part 2 for Arm 2). The opening of Part 3 is dependent upon antitumor activity observed in Part 2. Within each Arm, subjects will be monitored for clinical activity to enable early stopping for futility if sufficient antitumor activity is not demonstrated. For each Arm, the maximum planned enrollment in dose expansion is 40 subjects (Parts 2 and 3 combined). • **Arm 1:** Up to 10 eligible subjects with relapsed AML or previously treated MDS will initially be enrolled (Part 2). If ≥2 subjects achieve complete or partial remission per the European Leukemia Network (ELN) criteria or International Working Group (IWG) criteria for

	AML or MDS, respectively, Part 3 may be opened to enroll up to an additional 30 subjects. • **Arm 2:** Up to 10 eligible subjects with metastatic uveal melanoma will initially be enrolled (Part 2). If one of the following are observed in Part 2, then Part 3 may be opened to enroll up to an additional 30 subjects: o ≥1 complete or partial response as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; or, o ≥4 months median time to next treatment defined as the time from BPX-701 T cell infusion to initiation of next systemic therapy for the disease under study During Parts 1, 2, or 3, rimiducid (1 or more doses at 0.4 mg/kg) may be administered following BPX-701 T cell infusion in response to treatment-related toxicity (i.e., both on-target/off-tumor as well as on-target/on-tumor side effects). No formal hypothesis testing will be conducted. Rather, the statistical analysis will be descriptive and will summarize data by dose level/Part and tumor type (i.e., Arm 1 reported separately from Arm 2). Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Descriptive summaries of time to event data from Kaplan Meier estimates will include the number of events, number censored, medians, quartiles and 95% CIs. Graphical summaries of the data may be presented. All data will be listed for all subjects. The sponsor will establish a clinical data cutoff date for clinical study report analysis reporting 12 months after the last subject has received BPX-701 or after all subjects have discontinued the study, whichever comes first.
Study Objectives:	**Primary Objectives:** • **Phase 1 / Arm 1:** To characterize the safety and tolerability and to identify the MTD and/or the RDE of BPX-701 T cells administered to subjects with relapsed AML or previously treated MDS

	• **Phase 1 / Arm 2:** To characterize the safety and tolerability and to identify the MTD and/or RDE of BPX-701 T cells administered subjects with metastatic uveal melanoma • **Phase 2 / Arm 1:** To evaluate the remission rate following BPX-701 T cell infusion to subjects with relapsed AML or previously treated MDS • **Phase 2 / Arm 2:** To evaluate the antitumor activity of BPX-701 T cells administered to subjects with metastatic uveal melanoma **Secondary Objectives:** • To characterize the pharmacodynamics (PD) of BPX 701 T cells • To assess the response to rimiducid in those subjects with treatment-emergent BPX-701 toxicity • To characterize the pharmacokinetics (PK) of rimiducid after a single or repeat doses • To evaluate the clinical efficacy of BPX-701 T cells administered to subjects with relapsed AML or previously treated MDS • To evaluate the clinical efficacy of BPX-701 T cells administered to subjects with metastatic uveal melanoma • To assess the long-term safety of BPX-701 T cells **Exploratory Objectives:** • To assess the immunogenicity of BPX-701 T cells • To evaluate the frequency and level of PRAME expression in AML or MDS and uveal melanoma • To explore the relationship between BPX-701 PD biomarkers (e.g., BPX-701 T cell persistence, phenotyping, functional activity, tumor infiltration) and genetic and/or protein profiles in tumor tissue/bone marrow and peripheral blood • To explore the relationship between tumor tissue/blood-based immune biomarkers (including but not limited to PRAME) and clinical response or resistance to BPX-701 T cells
Inclusion Criteria:	1. Each subject (or their legally acceptable representative) must sign and date an informed consent form approved by the institutional review board/ethics committee, as appropriate, indicating that he/she understands the purpose of and procedures required for the study and are

	willing to comply. Consent is to be obtained prior to the performance of any study-specific procedures or tests that are not part of the standard of care for the subject's disease. 2. **Arm 1**: • MDS not responding to hypomethylation therapy or recurrence after initial response; or, • AML with disease relapse following first complete remission with intermediate or adverse genetics according to the ELN criteria – Subjects with a prior treatment history of stem cell transplant must be >100 days post-transplant with no evidence of active graft-versus-host disease and not requiring systemic immunomodulatory or immunosuppressive therapy defined as >10mg prednisone or equivalent per day and active use of a calcineurin inhibitor **Arm 2**: • Histologically or cytologically confirmed diagnosis of metastatic uveal melanoma • Measurable disease (at least one target lesion) per RECIST v1.1 • Adequate bone marrow function defined as: – Absolute neutrophil count ≥1,000/µL – Platelets ≥75,000/µL 3. Human leukocyte antigen (HLA)-A2.01 positive by local assessment 4. Documented positive myeloid blast or tumor expression of PRAME as determined by central testing of an available, representative bone marrow aspirate (fresh sample) or tissue specimen (formalin-fixed paraffin-embedded tissue, either from an archived sample or fresh biopsy) for Arm 1 and Arm 2, respectively 5. Absolute lymphocyte count ≥200/µL 6. Age ≥18 years 7. Life expectancy >12 weeks 8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 9. Subjects must have adequate venous access for apheresis or agree to use of a central line for apheresis collection

	10. Subject has adequate organ function: **Cardiac:** Left ventricular ejection fraction at rest must be ≥lower limit of institutional normal **Coagulation:** International normalized ratio ≤1.5 **Hepatic:** • Direct bilirubin ≤2x upper limit of normal (ULN), or ≤3x if due to Gilbert's disease • Aspartate aminotransferase and alanine aminotransferase ≤3 x ULN, or ≤5 x ULN if liver metastases are present **Renal:** Creatinine ≤1.5 x ULN 11. Before planned BPX-701 T cell infusion, as well as during the study, a female subject must be either: • Not of childbearing potential defined as: – Premenarchal, – Postmenopausal (>45 years of age with amenorrhea ≥12 months), – Permanently sterilized, – Otherwise incapable of pregnancy; or, • Of childbearing potential and agrees to use 2 highly effective methods of birth control for at least 12 months after lymphodepletion
Exclusion Criteria:	1. **Arm 1**: • Diagnosis of Acute Promyelocytic Leukemia • Primary refractory AML • Uncontrolled disseminated intravascular coagulation • Symptomatic or untreated central nervous system involvement by malignant cells • Peripheral blast count ≥20,000/µL 2. **Arm 2**: • Symptomatic, untreated or actively progressing central nervous system metastases. Subjects with prior brain metastases treated at least 2 weeks prior to the planned BPX-701 T cell infusion who are

	clinically stable and do not require chronic corticosteroid treatment are allowed • History of leptomeningeal disease 3. Ongoing toxicities related to prior anticancer therapy that have not resolved to Grade ≤1. Current unresolved Grade ≥2 non-hematologic toxicity may be allowed following discussion with and approval by the sponsor 4. Participation in any investigational drug study within 4 weeks prior to the planned BPX 701 T cell infusion 5. Chemotherapy (excluding hydroxyurea), targeted therapy, or radiotherapy (excluding palliative radiation) within 2 weeks, hydroxyurea within 1 week, or immunotherapy within 4 weeks prior to BPX-701 T cell infusion, other than salvage/lymphodepletion chemotherapy 6. Active autoimmune disease requiring immunosuppressive therapy. Subjects with vitiligo; type I diabetes; hypothyroidism, adrenal insufficiency, or hypophysitis only requiring hormone replacement; psoriasis not requiring systemic treatment or conditions not expected to recur; or history of Hashimoto's Thyroiditis on stable dose of thyroid hormone replacement therapy should not be excluded 7. Impaired cardiac function or clinically significant cardiac disease, including any of the following: • Symptomatic congestive heart failure requiring treatment; • Clinically significant cardiac arrhythmia; • Uncontrolled hypertension; • Acute myocardial infarction or unstable angina pectoris within 3 months prior to BPX-701 T cell infusion; or, • Marked limitation of physical activity due to symptoms, or unable to carry on any physical activity without discomfort (i.e., New York Heart Association Functional Class III-IV)

	8. Major surgical procedure, other than for diagnosis, within 4 weeks prior to BPX-701 T cell infusion, or anticipation of the need for a major surgical procedure during the study 9. Received a vaccine containing live virus within 4 weeks prior to the planned BPX 701 T cell infusion. Seasonal flu vaccines that do not contain live virus are permitted 10. Treatment with systemic chronic steroid therapy (prednisone >10mg daily or equivalent) within 7 days or 7 half-lives, whichever is shorter, prior to the planned apheresis date. Local steroid therapies (e.g., otic, ophthalmic, intra-articular or inhaled medications) are acceptable 11. Uncontrolled intercurrent illness including but not limited to poorly controlled hypertension or diabetes, or any medical condition determined by the investigator to be a risk for enrolling on the protocol 12. Uncontrolled infection requiring systemic therapy. Prior oral or IV antibiotics antifungals or antiviral medications must be discontinued at least 2 weeks prior to BPX-701 T cell infusion except for use of prophylactic antimicrobial agents 13. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test during Screening. Subjects with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening are eligible for the study if HBV DNA test is negative. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed 14. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test during Screening. The HCV RNA test will be performed only for patients who have a positive HCV test

	15. History of human immunodeficiency virus (HIV), or positive HIV test during Screening (unless not permitted by local regulations) 16. Subject is a woman of child-bearing potential is pregnant (positive serum β-human chorionic gonadotropin test at Baseline), planning to become pregnant within 12 months after lymphodepletion or is breastfeeding 17. Subject is a man who plans to father a child within 12 months after lymphodepletion 18. Known bovine product allergy 19. Malignant disease other than that being treated in this study. Exceptions to this exclusion are: • Malignancies that were treated curatively and have not recurred within 2 years prior to Screening • Completely resected basal cell and squamous cell skin cancers • Any malignancy considered to be indolent and that has never required therapy

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the curve
BLI	Bioluminescent imaging
CAR	Chimeric antigen receptor
CFR	Code of Federal Regulations
CID	Chemical inducer of dimerization
Cmax	Maximum concentration
CNS	Central nervous system
CR	Complete remission
CR_i	Complete remission with incomplete hematologic recovery
CR_{MRD-}	Complete remission without minimal residual disease
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebral spinal fluid
CT	Computed tomography
CTA	Cancer testis antigen
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
EC	Ethics committee

Abbreviation	Definition
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalogram
EFS	Event free survival
ELN	European Leukemia Network
EMA	European Medicines Agency
EOT	End of treatment
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FKBP	FK binding protein
GCP	Good Clinical Practice
GMCSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
GvHD	Graft-versus-host disease
HBV	Hepatitis B virus
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplant
HTLV	Human T-lymphotropic virus
HUS	Hemolytic-uremic syndrome
iCasp9	Inducible caspase-9
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive care unit

Abbreviation	Definition
IFN	Interferon
IL	Interleukin
INR	International normalized ratio
IWG	International Working Group
IRB	Institutional review board
irRC	Immune-related Response Criteria
ITT	Intent-to-treat
IV	Intravenous
kg	Kilogram
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LN2	Liquid nitrogen
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mg	Milligram
µL	Microliter
MLFS	Morphologic leukemia-free state
mm	Millimeter
MMSE	Mini mental status exam
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
msec	Millisecond
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCI	National Cancer Institute

Abbreviation	Definition
ng	Nanogram
NT	Non-transduced
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PD	Progressive disease
PFS	Progression free survival
PID	Primary immunodeficiency
PK	Pharmacokinetics
PR	Partial remission
PR	Partial response
PRAME	Preferentially expressed antigen in melanoma
PT	Prothrombin time
PTT	Partial thromboplastin time
qPCR	Quantitative polymerase chain reaction
RCR	Replication competent retrovirus
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Relapse free survival
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SDV	Source data verification
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
TCR	T-cell receptor

Abbreviation	Definition
TNF	Tumor necrosis factor
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
VASST	Vasopressin and Septic Shock Trial

1 INTRODUCTION

1.1 Preferentially Expressed Antigen in Melanoma (PRAME)

Cancer-testis antigens (CTAs) comprise a category of non-mutated genes expressed at high levels in germinal tissues and certain cancers including both hematologic and solid tumor malignancies, but which are absent from or detected at low levels in other tissues (Haqq 2005). CTA genes encode antigenic peptides that are naturally recognized by T lymphocytes. This, along with their limited expression pattern, makes CTA family members both an ideal target for anticancer immunotherapy as well as biomarkers for disease diagnosis and/or prognosis.

PRAME, or preferentially expressed antigen in melanoma, is one of the best characterized CTA family members. PRAME has a biological role in the regulation of retinoic acid signaling and acts to repress the retinoic acid receptor. Through this mechanism, PRAME likely confers a growth advantage to cancer cells although whether it is a driver or passenger gene remains to be established. In normal tissues, PRAME is expressed in the testis, adrenal gland, ovary, endometrium, and kidney epithelium and its expression levels are lower by more than 3 logarithmic series compared with that in tumor tissues (Ikeda 1997). Initially identified in 1997 by Ikeda and colleagues in melanoma tissue of cutaneous origin, PRAME was subsequently detected in both acute and chronic lymphoid and myeloid malignancies (van Baren 1998; Radich 2006) as well as uveal melanoma in addition to other solid tumor types including breast (Epping 2008), lung (Ikeda 1997), head and neck (Figueiredo 2006), and neurological cancers (Oberthuer 2004; Orlando 2018). High expression of PRAME has been associated with poor survival and shortened disease-free survival.

As is characteristic for CTAs, PRAME is naturally immunogenic. Through the T cell receptor (TCR) complex, ex vivo expanded T cells were shown to target PRAME peptide in context of human leukocyte antigen (HLA)-restricting elements (Amir 2011). Furthermore, PRAME has been shown to be a candidate for immunotherapy, inducing strong immune responses in healthy volunteers as well as patients with leukemia and cutaneous melanoma (Wadelin 2010). Together, these data provide clinical evidence that PRAME is a relevant target of interest for therapeutic intervention.

1.2 Study Rationale

BPX-701 is an investigational, controllable TCR immunotherapy candidate in early clinical development intended for the treatment of PRAME-expressing hematologic and solid tumor malignancies, specifically acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and uveal melanoma. The high-affinity TCR expressed within BPX-701 recognizes and binds to PRAME antigen presented by HLA-A2 on the surface of a cancer cell, initiating downstream signaling that leads to tumor cell apoptosis. Inclusion of an inducible safety switch within BPX-701 provides a mechanism to remove gene-modified T cells in response to uncontrollable treatment-emergent toxicity. Preclinical data with this first-in-clinic, inducible caspase-9

(iCasp9)-enabled TCR product candidate not only demonstrate antitumor activity against myeloma cells expressing PRAME/HLA-A2 but also illustrate the effectiveness and specificity of the safety switch in rapidly eliminating the genetically modified T cells.

It is hypothesized that the addition of an inducible "off" switch to BPX-701 provides a selective and controllable suicide signal, thereby mitigating the potential risk for treatment-related toxicity (i.e., both on-target/off-tumor as well as on-target/on-tumor side effects). Considering historical data that validate PRAME as a therapeutic target, this study aims to evaluate the safety, feasibility, and clinical activity of a PRAME-directed cellular therapy in selected oncology indications with high unmet medical need and without other disease-directed treatment options.

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 PRAME-Expressing Malignancies with Significant Unmet Medical Need

2.1.1 Leukemia

Leukemia is a cancer of the blood and bone marrow cells, affecting a group of white blood cells known as myeloid progenitors. MDS and AML exist along a pathology spectrum starting with early-stage MDS, which may progress to advanced disease. Across this spectrum, leukemia is characterized by an overproduction of immature blood cells. Disease onset has been associated with smoking, exposure to certain chemicals especially benzene, radiation exposure, inherited blood disorders, and certain genetic syndromes. Additionally, around 5-10% of patients with solid tumors that receive chemotherapy, radiation, or autologous stem cell transplantation as part of their anticancer treatment regimen eventually go on to subsequently develop chemotherapy-related MDS or AML even in circumstances where the original malignancy has resolved or stabilized.

Acute Myeloid Leukemia

It is estimated that 19,520 patients will be diagnosed with AML in 2018 (SEER 2018). While this represents only 1.1% of all new cancer cases, the 5-year mortality rate following initial diagnosis is 72.6% which highlights not only the aggressive pathology of this disease but also the need to develop effective therapies with the potential to impact long-term survival.

Rather than a single disease type, AML is a group of related diseases with a complex classification system based on leukemia cell morphology, chromosomal abnormalities, and molecular genetics and mutation profiling (Dohner 2017). Depending on the latter, patients are grouped into prognostic risk categories which help to inform treatment decisions. Generally, AML is difficult to treat, and current interventions come with significant toxicity. Initially, intensive chemotherapy combinations with or without targeted agent, if applicable, are administered to eliminate as many leukemia cells as possible. In addition, normal bone marrow cells are also depleted. This results in side effects that include increased risk of anemia, bleeding, infections, weight loss, bone pain, and an enlarged liver and spleen and require intensive supportive care management with antibiotics

and recurring blood product transfusions. If initial therapy is effective in reducing tumor burden and remission is achieved, a hematopoietic stem cell transplant (either autologous or allogeneic) with or without high-dose chemotherapy is often pursued not only to destroy any leftover leukemia cells but also prevent disease relapse.

For patients initially treated with aggressive induction chemotherapy, between 20-40% will not obtain a remission and are considered to have primary refractory disease (Cheson 2004). The prognosis for these patients as well as those with disease recurrence post-transplant are poor. Indeed, a retrospective analysis study of 594 patients with AML undergoing second salvage therapy after standard treatment, which includes stem cell transplantation, reported a median survival of 1.5 months with a 1-year survival of 8%. Subgroup analysis of those attaining remission (13%) showed only a 7-month median remission duration. Multivariate analysis revealed several poor prognostic features including age >60, initial remission duration <12 months, and second remission duration <6 months (Giles 2005). Importantly, standard therapies do not appear to favorably impact patients who relapse in <12 months (Kumar 2002).

Elderly patients not eligible for intensive chemotherapy or transplant generally have poor outcomes and remain a significant therapeutic challenge. Beyond best supportive care or off-label, low-dose use of certain chemotherapy drugs, no standard treatment is currently available. Out of those with sufficient performance status to receive chemotherapy, 30-40% will achieve a remission with standard induction yet the median survival approximates only 10 months (Oran 2012).

PRAME overexpression has been assessed in AML and was shown to be present in approximately 32-55% of patients depending on the study (Ding 2012; Goswami 2014; Qin 2009; van Baren 1998). In acute leukemia cells, inhibition of PRAME resulted in apoptosis suggesting it plays a key role in tumorigenesis and disease progression (Tanaka 2011). The clinical relevance is less clear as some studies have reported an association between high PRAME expression and favorable cytogenetics (van Baren 1998) as well as survival outcomes (Greiner 2006; Tajeddine 2008), whereas other studies have not (Paydas 2005; Guinn 2009).

Myelodysplastic Syndrome

The American Cancer Society estimates approximately 10,000 patients are diagnosed annually with MDS (American Cancer Society 2018), although incidence rates reported by others is much higher. Age and gender are key risk factors for MDS, with onset most commonly observed in females at least 70 years old. Other risk factors are similar to those reported for AML. Like AML, patients with MDS are classified into different risk groups using a formal prognostic scoring system based on bone marrow morphology, chromosomal abnormalities, and peripheral blood cell counts. The resulting score determines overall risk category thereby informing treatment strategy.

The standard of care for intermediate- or high-risk MDS is azacitadine or decitabine either with (for candidates with good performance status and an eligible matched donor) or without an

allogeneic hematopoietic stem cell transplant. For patients with relapse or failure in response to initial hypomethylation-based therapy, overall prognosis is poor with no evidence of benefit of any available treatment relative to best supportive care. Moreover, standard algorithms recommend clinical trials for disease management in this setting (Sekeres 2014).

PRAME expression in MDS has been studied as a marker for higher risk disease with worse outcomes although this observation has not been validated in larger cohorts of patients. Data from Qian et al showed that 11 of 56 patients (19.6%) with MDS had *PRAME* gene promoter hypomethylation, a frequency that was higher in the context of abnormal cytogenetics and higher blast counts (Qian 2011). In this study, PRAME methylation status was predictive for overall survival with a 50% survival time of 11 versus 26 months for those with hypomethylated versus methylated *PRAME*, respectively. Other groups have reported similar findings in a study of 73 MDS patients that identify a correlation between high PRAME expression and poor survival (Liberante 2013).

Collectively these observations (i.e., PRAME hypomethylation is associated with worse outcomes along with the standard use of hypomethylating agents in early treatment lines) together suggest that a PRAME-directed agent may be uniquely poised to provide potential clinical benefit to intermediate-to-high risk MDS patients with relapse or progression after initial therapy.

2.1.2 Uveal Melanoma

Melanoma of the uveal tract (iris, ciliary body, and choroid), though rare, is the most common primary intraocular malignancy in adults. Uveal melanoma is biologically different from cutaneous melanoma. The American Cancer Society estimates approximately 3500 people will be diagnosed with ocular cancer in 2018 (American Cancer Society 2018) with risks for disease onset being higher for those of Caucasian ethnicity with lighter eye color. While treatment of primary uveal melanoma, usually with surgery or radiotherapy, is almost invariably successful, cumulative rates of metastases at 5, 10, and 15 years after treatment were 25%, 34%, and 50% respectively (Diener-West 2005; Kujala 2003). The 5-year survival rate for metastatic uveal melanoma is about 15% (American Cancer Society 2018). No therapy has demonstrated a survival advantage for patients with metastatic uveal melanoma making this disease one of the few remaining malignancies for which there are no effective treatments in the metastatic setting. Thus, there is an urgent need to develop novel, proven treatments for this disease.

PRAME is a known prognostic biomarker of metastatic risk in patients with uveal melanoma (Field 2016). As for AML or MDS, PRAME has been proposed as a potential therapeutic target in uveal melanoma given its lack of expression in normal versus malignant tissues. Indeed, a retrospective study showed 69% of patients with metastatic uveal melanoma expressed PRAME (Gaugin 2017). This same trial demonstrated that HLA-A2-restricted PRAME-specific T cells recognized and were active against PRAME-positive uveal melanoma cell lines. Experimental vaccines targeting PRAME have been investigated for the treatment of cutaneous melanoma

(NCT01149343) and other PRAME-expressing solid tumors (NCT01853878). Together these data provide scientific rationale for evaluating the potential clinical benefit of PRAME-directed immunotherapy in metastatic uveal melanoma where no approved standard treatment currently exists.

3 INVESTIGATIONAL PRODUCTS: BPX-701 AND RIMIDUCID

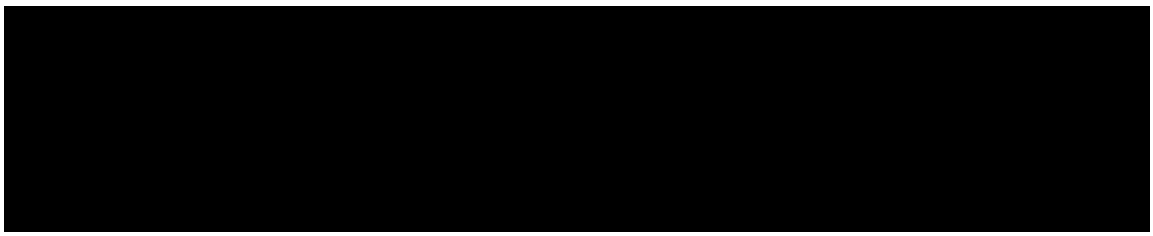
For the most comprehensive nonclinical and clinical information regarding BPX-701 and rimiducid, refer to the latest version of the Investigator Brochure for each product (BPX-701 Investigator Brochure, Rimiducid Investigator Brochure).

3.1 BPX-701: PRAME TCR Immunotherapy

BPX-701 is a PRAME-directed, genetically modified, autologous T cell product candidate that binds to PRAME-expressing cells. In an HLA-A2.01-restricted manner, BPX-701 targets PRAME with an αβ TCR containing a traditional CD3ζ cytoplasmic signaling domain (Figure 1). The PRAME TCR selected for inclusion into BPX-701 has a natural high affinity, but this has not been further enhanced during product development. Further analysis of this T cell clone isolated from a patient with AML showed high reactivity against a panel of PRAME-positive tumor cells including cutaneous melanoma, sarcoma, and AML. No reactivity to normal cell types was observed except for low reactivity against kidney epithelial cells and intermediate reactivity against mature dendritic cells, a finding that is consistent PRAME expression in normal tissues (Ikeda 1997).

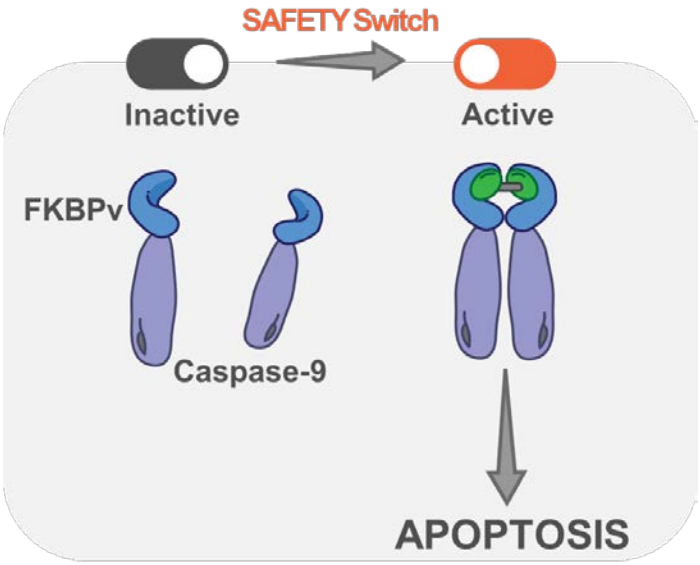
In addition to the PRAME TCR, BPX-701 T cell therapy is engineered to express an inducible caspase-9 (iCasp9) safety switch comprised of two FK binding proteins (FKBP) in-frame with signaling domain from caspase-9. The rationale for the molecular design as well as the *in vitro* and *in vivo* characterization of this inducible safety switch are described elsewhere (Straathof 2005).

Figure 1: BPX-701 Retroviral iCasp9 Vector Construct



iCasp9 functions as a molecular switch to induce apoptosis of T cells in the presence of the small molecule dimerizer rimiducid (Figure 2). The tandem FKBP domains provide a ligand dimerization scaffold, which induces iCasp9 in a rimiducid-dependent manner (Straathof 2005).

Figure 2: iCaspase-9 Safety Switch



Several historical reports have demonstrated the clinical benefit of an adoptive cell therapy approach using ex vivo expanded T cells that are restricted against both an HLA antigen and a selected tumor peptide depending on the disease under study. While BPX-701 employs a similar mechanistic approach based off HLA-A2.01 and the PRAME TCR, this is the first example of a PRAME-directed autologous cell product candidate that is also designed to leverage the clinical utility of an inducible safety switch in response to treatment-emergent, uncontrollable toxicity. The latter is hypothesized to be a potential differentiating factor for BPX-701 relative to other cell therapy alternatives (e.g., chimeric antigen receptor-T [CAR-T] cells). Given the high frequency of PRAME overexpression in metastatic uveal melanoma and the current lack of any approved therapy, the rational design of BPX-701 suggests that it may have an opportunity to provide clinical benefit while also mitigating the risk of associated treatment side effects not only in this solid tumor disease setting but also for hematologic malignancies.

3.1.1 Summary of Preclinical Experience: BPX-701

3.1.1.1 *In Vitro* Studies

In preclinical studies, PRAME-specific clones showed high reactivity against a panel of PRAME positive tumor cell lines, metastatic melanoma, sarcomas and neuroblastoma tissues, and no reactivity against normal cell types, with the exception of low reactivity against kidney epithelial cells and intermediate reactivity against mature dendritic cells.

In vitro studies showed that T cells expressing the PRAME-specific BPX-701 TCR recognized a variety of tumor cell lines and primary AML blasts, positive for both PRAME and HLA-A2, as indicated by cytokine (i.e., interferon-γ) production (Amir 2011). Additional preclinical results

demonstrate complete elimination of BPX-701 cells in response to rimiducid (BPX-701 Investigator Brochure).

3.1.1.2 *In Vivo* Studies

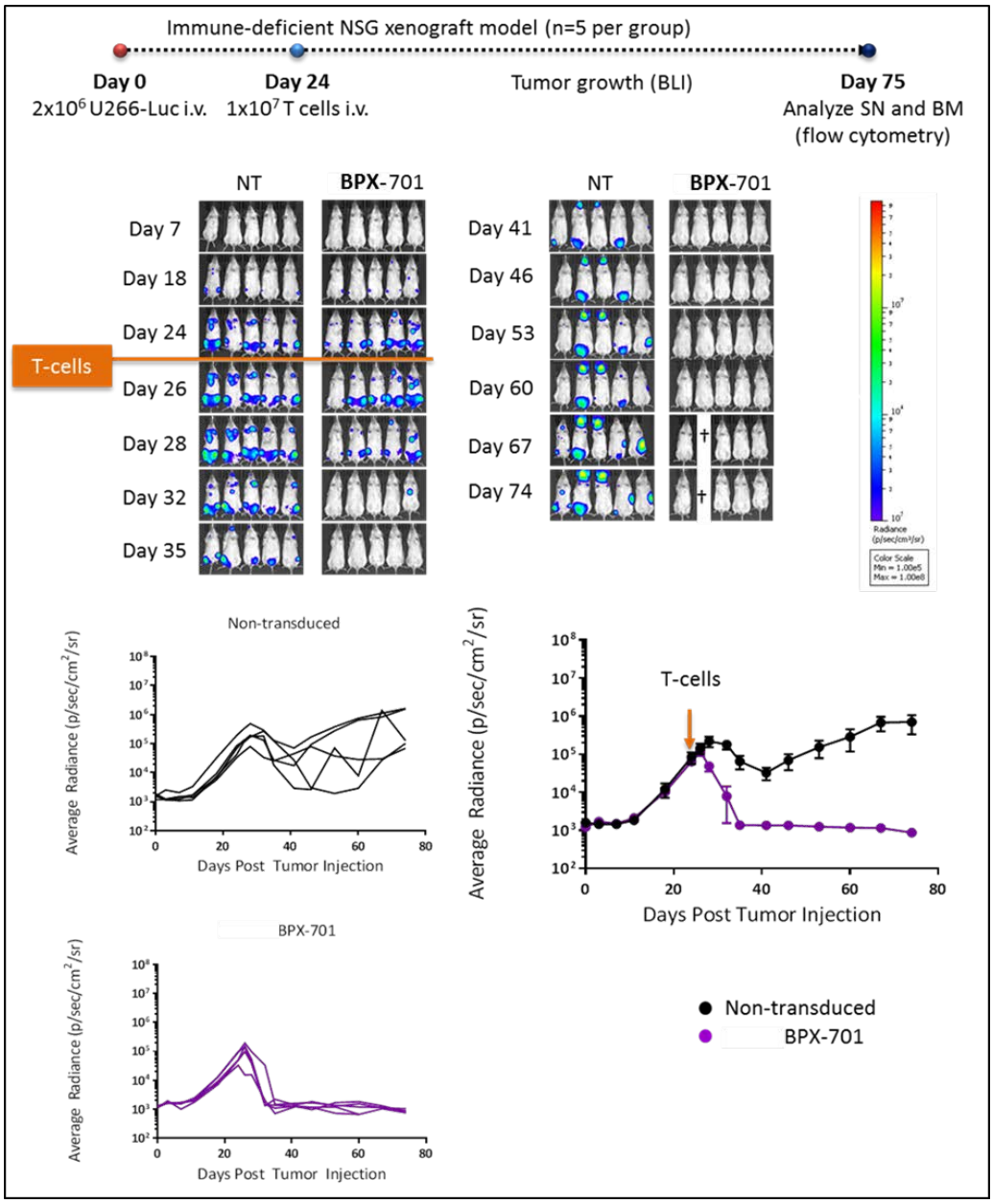
Although immunodeficient mouse models have historically not been helpful in predicting clinically relevant toxicity, such *in vivo* models have been utilized to demonstrate the antitumor activity of BPX-701 T cells as well as the functional elimination of BPX-701 T cells by rimiducid. Collectively, these data demonstrate that BPX-701 cells are effective against PRAME-expressing tumor cells and that iCasp9 effectively eliminates transduced T cells following rimiducid treatment. Results of these experiments are briefly described below.

Antitumor activity of normal human T cells modified with PRAME TCR and iCasp9

PRAME-expressing myeloma tumors were established in immunodeficient (NOD/SCID/γcnull) NSG mice by tail vein injection of 2 x 10^6 U266-EGFP-luciferase (U266-EGFPluc) tumor cells per animal. On Day 24 following successful tumor engraftment, mice received either 1 x 10^7 nontransduced (NT) T cells (n=5) or an equivalent dose of BPX-701 T cells (n=5) (Bellicum Report BEL-R&D-RP-0014). Tumor size was evaluated weekly using an *in vivo* imaging system.

Treatment with a single dose of BPX-701 T cells resulted in complete myeloma tumor elimination in less than two weeks after administration and controlled tumor growth for over 50 days, whereas injection of NT cells failed to affect tumor growth (Figure 3). Using average radiance as a surrogate marker of tumor burden, mice that received NT cells had ~800-fold more U266-EGFPluc cells than those that were treated with BPX-701; this difference in tumor burden reached statistical significance within 8 days (p=0.002). These data indicate that a single injection of 1 x 10^7 BPX-701 T cells but not NT cells results in antitumor activity against PRAME-positive myeloma tumors *in vivo*.

Figure 3: *In vivo* imaging of myeloma tumors following treatment with BPX-701

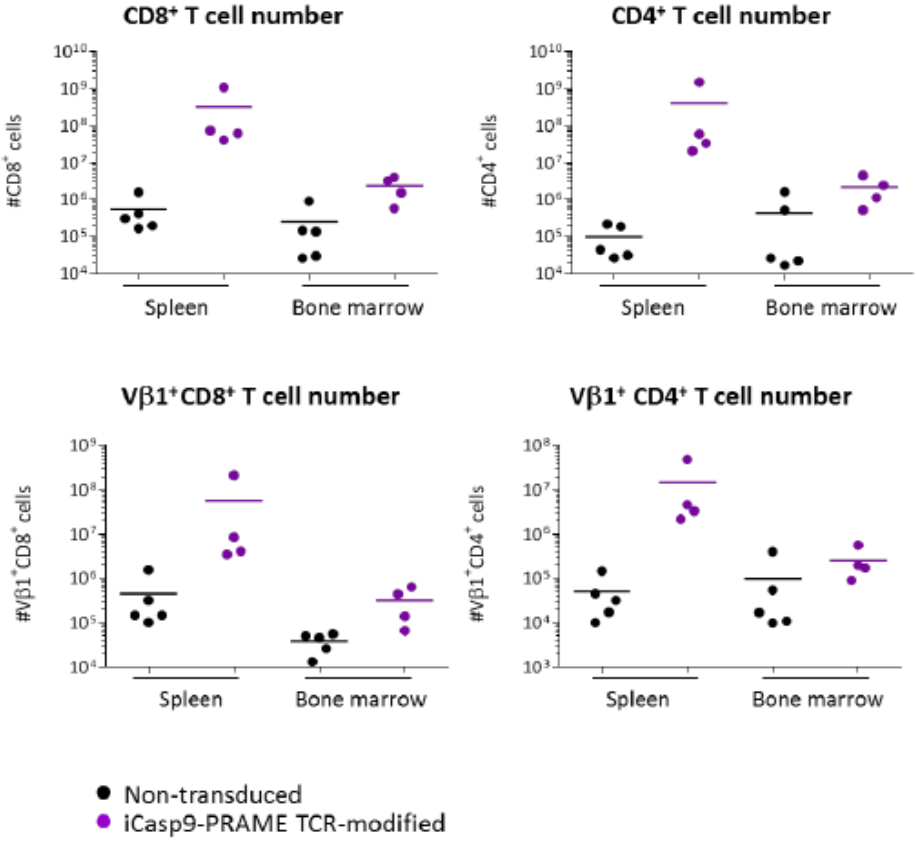


In vivo *persistence of T cells modified with PRAME TCR and iCasp9*

Spleen and bone marrow cells were harvested on Day 51 post-injection from mice treated with NT or BPX-701 T cells as described above (Bellicum Report BEL-R&D-RP-0014). Cells were counted and analyzed by flow cytometry for Vβ1 expression (BPX-701 transduction marker) on CD4 and CD8 T cells. Despite the lack of detectable tumor by *in vivo* imaging, BPX-701 T cells persisted in the spleen and bone marrow (Figure 4). Approximately 600-fold more total CD8+

T cells and ~130-fold more Vβ1+CD8+ T cells were observed in the spleens of mice that received BPX-701 T cells than those treated with NT cells. Thus, following a single injection, BPX-701 T cells exhibit measurable *in vivo* persistence >7 weeks.

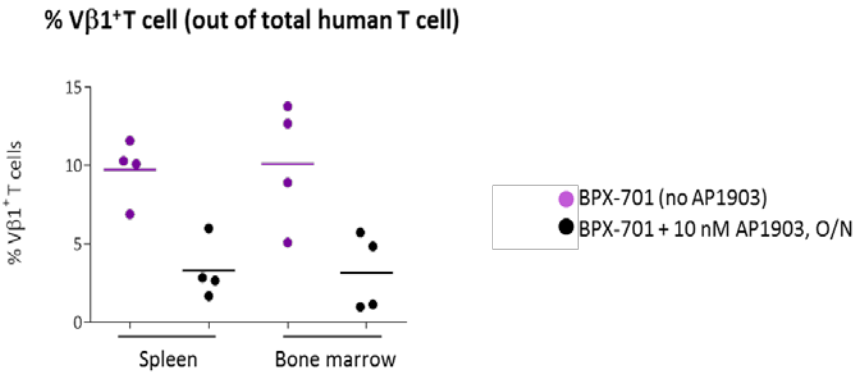
Figure 4: BPX-701 modified T cells persist *in vivo* at least 7 weeks



Persisting T cells modified with PRAME TCR and iCasp9 are sensitive to rimiducid

To evaluate the functionality of iCasp9 in persisting BPX-701 T cells, a fraction of spleen and bone marrow cells from BPX-701-treated mice as described above were isolated on Day 51 post-injection and cultured overnight with or without rimiducid (Bellicum Report BEL-R&D-RP-0014). Rimiducid significantly reduced the fraction of Vβ1+ T cells recovered from both spleen and bone marrow ($p<0.05$). These data show that iCasp9 gene function is both maintained over time and is not affected by antitumor activity (Figure 5).

Figure 5: Active, persisting BPX-701 T cells remain sensitive to rimiducid after 7 weeks



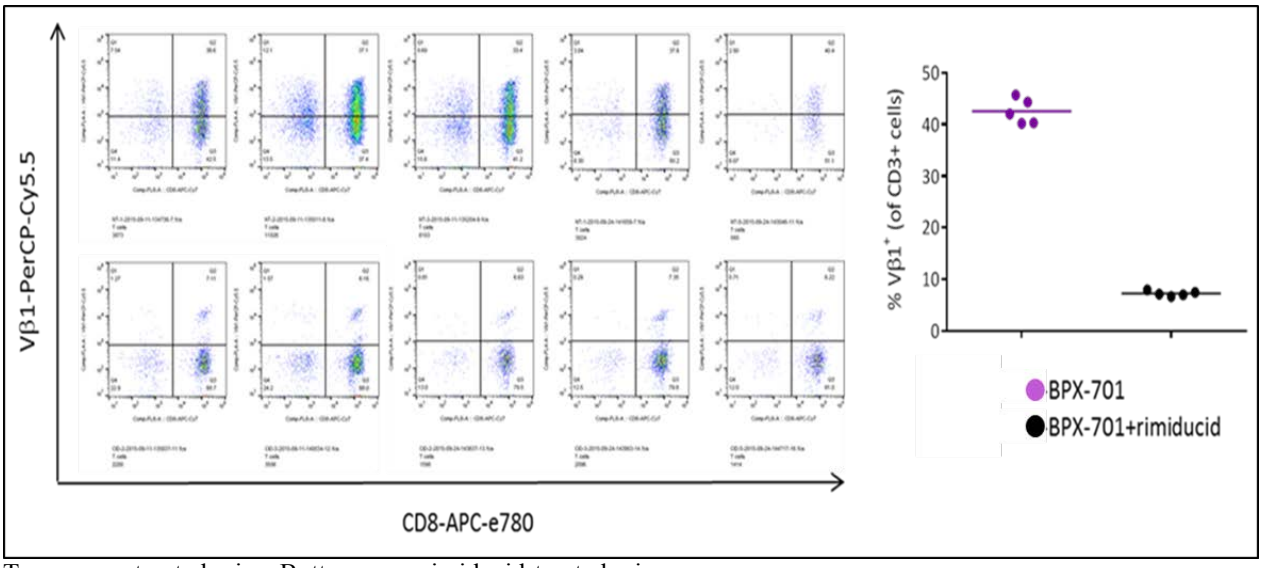
AP1903 = rimiducid

***iCasp9 is a functioning safety switch in BPX-701 T cells* in vivo**

Following tail-vein injection into immunodeficient (NOD/SCID/γcnull) NSG mice, BPX-701 T cells (1 x 10^7) were detected in the spleen as early as 24 hours and further increased in number at 48 hours post-injection (Bellicum Report BEL-R&D-RP-0015). Therefore, the latter time point was chosen to assess the effect of rimiducid on BPX-701 cell viability *in vivo*.

Rimiducid (5 mg/kg) was administered to NSG mice (n=8) by intraperitoneal injection following treatment with BPX-701 T cells while an equivalent number of mice (n=8) were untreated (i.e., mice received BPX-701 T cells alone). Spleens harvested 24 hours following intraperitoneal injection were analyzed by flow cytometry. Although NT cells were detected in 5 out of 8 mice per treatment group, the frequency of BPX-701 T cells in rimiducid-treated mice was significantly reduced compared to untreated mice (7.3 ± 0.2% versus 42 ± 1.1%, $p<0.0001$; Figure 6).

Figure 6: Rimiducid-mediated elimination of BPX-701 T cells *in vivo*



Top row: untreated mice; Bottom row: rimiducid-treated mice

3.2 Summary of Clinical Experience: BPX-701

BPX-701 is a first-in-class, suicide-inducible T cell therapy for subjects with PRAME-expressing hematologic or solid tumor malignancies with high unmet medical need. This study is the first experience with BPX-701 T cells in human subjects; therefore, no prior clinical data are available.

3.3 Rimiducid: Dimerizer Drug

Rimiducid is a member of a new class of synthetic lipid-permeable compounds termed chemical inducers of dimerization or CIDs. Rimiducid is a small molecule, high affinity ligand (~0.1 nM) that functions to promote cross-linking and activation of engineered proteins inside cells. By chemical design, rimiducid has no known natural biologic target; ligand binding is restricted to a mutated signaling domain of the human protein FKBP (Rimiducid Investigator Brochure).

3.3.1 Summary of Clinical Experience: Rimiducid

Refer to the Investigator Brochure for a summary of preclinical studies as well as additional information regarding clinical experience with rimiducid (Rimiducid Investigator Brochure). An abbreviated summary of clinical results is provided below.

Phase I Study in Healthy Volunteers

The safety and pharmacokinetics of rimiducid were previously evaluated in a single-blind, placebo-controlled phase I clinical trial in 28 healthy adult volunteers (Iuliucci 2001). Eligible subjects received either a single dose of rimiducid, placebo, or normal saline administered by

intravenous infusion over 2 hours. Ascending dose levels of rimiducid (0.01, 0.05, 0.1, 0.5, and 1.0 mg/kg) were investigated.

Rimiducid was shown to be safe and well tolerated at all dose levels and demonstrated a favorable pharmacokinetic profile (Iuliucci 2001). No drug-related adverse events were observed except for facial flushing at the 1.0 mg/kg dose level. No adverse events met the protocol definition of dose-limiting toxicity (DLT). Rimiducid plasma levels were directly proportional to the administered dose, with mean C_{max} values ranging from approximately 10 to 1275 ng/mL over the 0.01 to 1.0 mg/kg dose range. Following the infusion period, blood concentrations revealed a rapid distribution phase, with plasma levels being reduced to approximately 18%, 7%, and 1% of the maximal concentration at 0.5, 2, and 10 hours post-infusion, respectively. The mean terminal half-life varied somewhat with dose, ranging from 3.92 hours at 0.05 mg/kg to 12.0 hours at 1.0 mg/kg, and was determined to likely be a function of assay sensitivity.

Phase I and II Studies in Patients

The safety and pharmacokinetics of rimiducid have been similarly evaluated in early clinical trials in pediatric and adult patients with primary immunodeficiencies (PID) or hematologic malignancies. In a combined analysis from two phase 1/2 studies (NCT02065869; NCT03301168), 59 children with PID received an investigational T cell product containing the iCasp9 safety switch following a polyclonal α/β T-cell and B-cell-depleted HLA-haploidentical hematopoietic stem cell transplant (HSCT) as a means not only of facilitating transplant engraftment and preventing infections but also with the unique ability to promptly and durably resolve graft-versus-host disease (GvHD) symptoms (Pagliara 2018). Nineteen patients developed acute GvHD; of these, 7 received at least 1 dose of rimiducid for treatment-related side effects not responsive to standard of care intervention or for visceral involvement. Overall, response to rimiducid was >80% in evaluable PID patients. Rimiducid induced rapid (within 7-10 days) and significant (>50%) decreases in the frequency of peripheral iCasp9 cells. No adverse events related to rimiducid were reported.

In a parallel phase 1/2 study (NCT02065869), 38 children with first complete remission (CR1) high risk and CR2 AML were treated with the same investigational T cell product containing the iCasp9 safety switch described previously. At the time of HSCT, eligible patients were infused with adjuvant polyclonal iCasp9 T cells derived from an HLA-partially matched family donor after negative selection of α/β T-cells. The cumulative incidence of Grade II-IV and Grade III-IV acute GvHD within 100 days of HSCT was 2.6% and 0%, respectively (Kapoor 2018). Eleven patients developed GvHD (acute or chronic); of these, 5 received at least 1 dose of rimiducid for GvHD not responsive to corticosteroids. Four out of 5 patients achieved complete resolution of GvHD after administration of rimiducid (80% response rate); time to complete response ranged from 7 to 55 days. T-cell kinetics in response to rimiducid were similar to what was observed in patients with PID. No patient experienced a relapse after administration of rimiducid. No adverse events related to rimiducid were reported.

4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
• **Phase 1 / Arm 1:** To characterize the safety and tolerability and to identify the maximum tolerated dose (MTD) and/or the recommended dose for expansion (RDE) of BPX-701 T cells administered to subjects with relapsed AML or previously treated MDS	• Incidence of dose-limiting toxicity, frequency and severity of adverse events (AEs) and serious AEs (SAEs), changes from baseline in safety parameters
• **Phase 1 / Arm 2:** To characterize the safety and tolerability and to identify the MTD and/or RDE of BPX-701 T cells administered subjects with metastatic uveal melanoma	• Incidence of dose-limiting toxicity, frequency and severity of treatment emergent AEs and SAEs, changes from baseline in safety parameters
• **Phase 2 / Arm 1:** To evaluate the remission rate following BPX-701 T cell infusion to subjects with relapsed AML or previously treated MDS	• **AML:** Percentage of subjects with complete remission (CR; including CR_{MRD-}, CR, CR_i) or partial remission (PR) as determined by the investigator according to the European LeukemiaNet (ELN) criteria for AML • **MDS:** Percentage of subjects with CR (including marrow CR) or PR as determined by the investigator according to the International Working Group (IWG) criteria for MDS
• **Phase 2 / Arm 2:** To evaluate the antitumor activity of BPX-701 T cells administered to subjects with metastatic uveal melanoma	• Percentage of subjects with complete response (CR) or partial response (PR) determined by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• To characterize the pharmacodynamics (PD) of BPX-701 T cells	• Expansion and persistence of peripheral BPX-701 T cells over time, change from baseline in serum cytokines
• To assess the response to rimiducid in those subjects with treatment-emergent BPX-701 toxicity	• Time to event resolution and persistence of peripheral BPX-701 T cells after rimiducid administration
• To characterize the pharmacokinetics (PK) of rimiducid after a single or repeat doses	• Serum concentration-time profiles and PK parameters (including Cmax and AUC)
• To evaluate the clinical efficacy of BPX-701 T cells administered to subjects with relapsed AML or previously treated MDS	• **AML:** Percentage of subjects with stable disease (SD), and morphologic leukemic-free state (MLFS); time to next treatment, relapse-free survival, event-free survival, and overall survival per the ELN criteria for AML • **MDS:** Percentage of subjects with SD, cytogenetic response, and hematologic improvement; time to next treatment, relapse-free survival, event-free survival, and overall survival per the IWG criteria for MDS
• To evaluate the clinical efficacy of BPX-701 T cells administered to subjects with metastatic uveal melanoma	• Percentage of subjects with disease control; progression-free survival, time to next treatment, and duration of response; and, overall survival per RECIST v1.1
• To assess the long-term safety of BPX-701 T cells	• Proportion of subjects with detectable replication competent retrovirus in peripheral blood up to 15 years following BPX-701 T cell infusion

OBJECTIVES	ENDPOINTS
Exploratory	
• To assess the immunogenicity of BPX-701 T cells	
• To evaluate the frequency and level of PRAME expression in AML or MDS and uveal melanoma	
• To explore the relationship between BPX-701 PD biomarkers (e.g., BPX-701 T cell persistence, phenotyping, functional activity, tumor infiltration) and genetic and/or protein profiles in tumor tissue/bone marrow and peripheral blood	
• To explore the relationship between tumor tissue/blood-based immune biomarkers (including but not limited to PRAME) and clinical response or resistance to BPX-701 T cells	

5 STUDY RATIONALE AND CLINICAL DESIGN

5.1 Overview of Rationale and Design

While adoptive T cell therapies have yielded high objective response rates in blood cancers, serious and sometimes fatal side effects have arisen as a result of treatment. For example, the commercially available CD19-directed CAR-T cell treatments KYMRIAH™ and YESCARTA™ both carry black box warnings associated with the risk of life-threatening cytokine release syndrome (CRS) and neurological toxicities (Kymriah Package Insert 2018; Yescarta Package Insert 2017). Among clinical trial patients who died due to any cause after receiving these cell therapies in an investigational setting, the majority had ongoing CRS at time of death (Kymriah Package Insert 2018; Neelapu 2018). Furthermore, the frequency of Grade ≥3 CRS and neurological toxicities in subjects with B-cell lymphoma treated in pivotal studies for KYMRIAH™ and YESCARTA™ ranged from 13-23% and 18-28%, respectively. A strategy to selectively modulate donor T cell function *in vivo* could potentially overcome these potential limitations thereby significantly improving the safety profile.

Preclinical data illustrate both the *in vivo* antitumor activity of BPX-701 against PRAME expressing-myeloma cells as well as the functionality of the iCasp9 safety switch in response to the dimerizer rimiducid. The latter rapidly eliminated PRAME-TCR-specific T cells *in vivo* within 24 hours and therefore may serve as a mechanism to help alleviate the risk of BPX-701-related side effects. Prior clinical evaluation of rimiducid in healthy volunteers (Iuliucci 2001) as well as in transplantation studies for mitigation of GvHD showed this dimerizer to be safe and effective and supports its use in combination with BPX-701 T cells (Kapoor 2018; Pagliara 2018), as needed, for the treatment of relapsed AML or previously treated MDS, as well as advanced uveal melanoma.

The goal of this study is to characterize the safety, feasibility, and clinical activity of BPX-701, a genetically modified autologous T cell product incorporating an HLA-A2.01-restricted PRAME-directed TCR and an inducible iCasp9 safety switch, when administered to subjects with relapsed AML (Arm 1), previously treated MDS (Arm 1), or metastatic uveal melanoma (Arm 2). Arms 1 and 2 are intended to be conducted in parallel; however, the overall assessment of BPX-701 safety, feasibility, and clinical activity observed in Arm 1 will be evaluated independently from Arm 2. For each Arm, the study will be comprised of multiple parts:

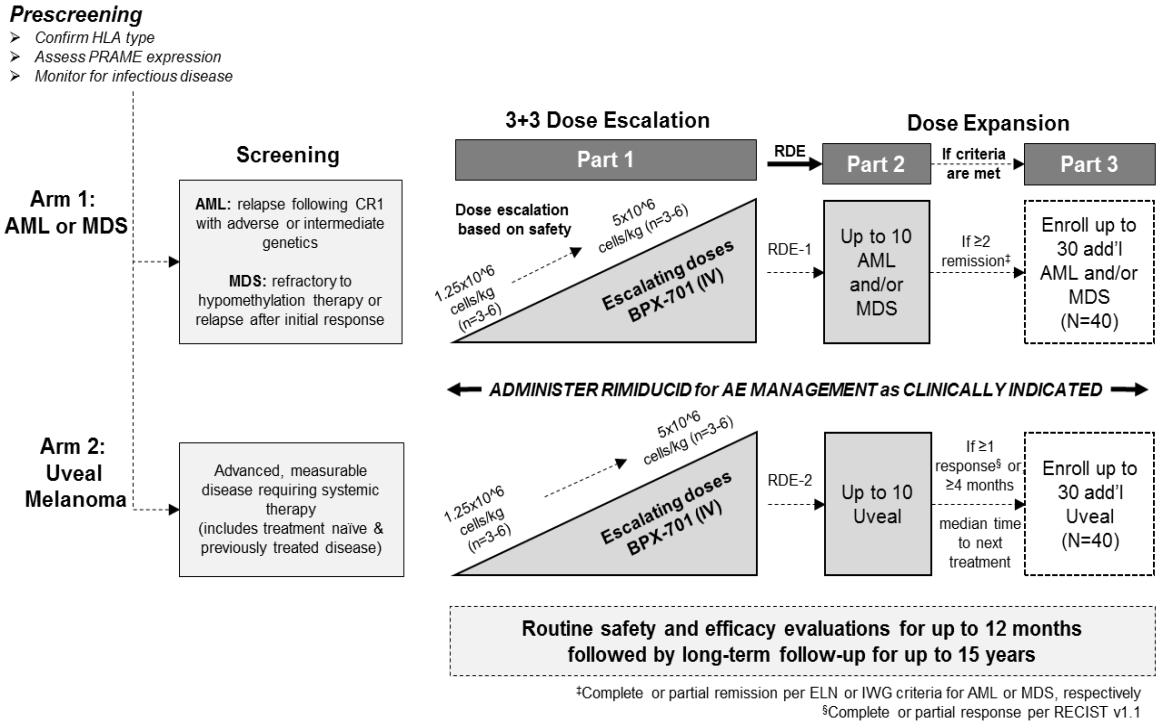
- **Part 1 (Phase 1): Cell dose escalation** to identify the maximum dose of BPX-701 T cells (escalating doses from 1.25 x 10^6 cells/kg up to 5.0 x 10^6 cells/kg to be explored)

- **Parts 2 and 3 (Phase 2): Dose expansion** to assess the safety, pharmacodynamics (including BPX-701 T cell persistence and response to rimiducid as applicable), and clinical activity at the recommended dose identified in Part 1

- During Parts 1, 2, or 3, rimiducid (1 or more doses at 0.4 mg/kg) may be administered following BPX-701 T cell infusion in response to treatment-emergent toxicity (i.e., both on-target/off-tumor as well as on-target/on-tumor side effects)

A diagram of the study design is provided in Figure 7. Study eligibility will be determined based on sequenced Prescreening/Screening assessments. Accrual of eligible subjects will begin in Part 1. Dose escalation decisions for each Arm will be made independently. Therefore, more than one RDE may be defined (i.e., RDE-1 for Arm 1 and RDE-2 for Arm 2). Once an RDE is determined in Part 1, enrollment in Part 2 will be initiated. Part 3 will commence provided sufficient clinical activity is observed in Part 2. Alternately, if treatment-emergent BPX-701 toxicity is not responsive to rimiducid, there is an unfavorable change to risk/benefit, pharmacodynamic responses are deemed insufficient, or BPX-701 clinical activity is considered inadequate, Parts 2 and 3 (i.e., Arm 1, Arm 2, or both) may not be initiated and/or the study may be prematurely terminated prior to completing the planned enrollment.

Figure 7: Study Design Schematic



5.2 BPX-701 T Cell Starting Dose Rationale

For Arm 1 and Arm 2, the recommended initial starting dose for BPX-701 T cells is 1.25 x 10^6 cells/kg. This starting dose was chosen based on preclinical studies and for consistency with other experimental TCR immunotherapies directed against alternate antigens expressed by solid tumors and/or hematologic malignancies. While some of these trials reported safe infusion of cell doses as high as 1 x 10^{10} (Rapoport 2015), others have observed dose-limiting toxicity at 2 x 10^8 cells (Parkhurst 2011) as well as patient fatalities upon infusion of larger cell numbers (i.e., >1 x 10^9) (Linette 2013; Morgan 2013; van den Berg 2015). Although no acute toxicities following BPX-701 infusion were observed in preclinical animal studies at a dose of 1 x 10^7 T cells, a lower dose was selected for initial safety evaluation in humans and allows for escalation to higher cell dose levels provided a favorable safety profile is maintained. In addition, and unique from previously evaluated TCR immunotherapies, BPX-701 contains an inducible safety switch that provides for rapid elimination of T cells in the event of treatment-emergent toxicity.

5.2.1 Rimiducid

Rimiducid will be administered at a fixed dose of 0.4 mg/kg in this study. Prior clinical experience with IV administration of doses up to 1.0 mg/kg with no evidence of clinical intolerability is described elsewhere (Iuliucci 2001) and provides rationale this recommended dose in accordance with the Investigator Brochure (Rimiducid Investigator Brochure).

5.3 Dose-Limiting Toxicity

Toxicities will be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). The evaluation period for defining DLT and informing dose escalation decisions is from the start of the BPX-701 infusion on Day 0 through Day 28. However, toxicities that occur outside of this window may be considered in decisions regarding the RDE.

Dose-limiting toxicity is defined as any of the following unless clearly due to disease progression or extraneous causes:

- Any treatment-emergent CTCAE Grade 4 or 5 CRS
- Any treatment-emergent CTCAE Grade 3 CRS that does not resolve to Grade ≤2 within 7 days
- Any treatment-emergent autoimmune toxicity Grade ≥3
- CTCAE Grade ≥3 infusion reaction
- Any other treatment-emergent CTCAE Grade ≥3 organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing or due to the underlying malignancy that does not resolve to Grade ≤2 within 7 days (except treatment-emergent CTCAE Grade ≥3 hematologic toxicity observed in subjects with AML/MDS)

Events that meet the definition of DLT are considered adverse events of special interest for this study. Refer to Section 9.8 for reporting procedures.

5.4 Clinical Design

5.4.1 Part 1 (Phase 1): Cell Dose Escalation

Part 1 is a Cell Dose Escalation phase designed to determine the appropriate BPX-701 T cell dose for expansion using a 3+3 dose escalation design. Enrollment in sequential dose escalation cohorts will proceed as described in Table 1.

For each of Arms 1 (AML and MDS) and 2 (uveal melanoma), Cohort 3 (1.25 x 10^6 cells/kg) is the initial starting cohort for cell dose escalation decisions in Part 1. Cohorts of at least 3 and up to 6 evaluable subjects will be treated with escalating doses of BPX-701 T cells on Day 0 until the MTD or RDE is achieved. Planned doses of BPX-701 T cells are detailed in Table 2. The initial 3 subjects in each of Arms 1 and 2 (Cohort 3) will be enrolled sequentially, with the second and third subjects enrolled no sooner than 1 month (28 days) after the prior subject has been infused with BPX-701. The first patient of the next cohort will be infused no sooner than 1 month (28 days) after the last patient in Cohort 3 has been infused. All subsequent patients will be enrolled in the usual manner for a 3+3 design.

Subjects will be considered evaluable for dose escalation assessment if the scheduled dose of BPX-701 T cells was administered, the subject received a sufficient number of BPX-701 T cells to satisfy dose level requirements, and the DLT evaluation period (Day 0 through Day 28) was completed, or the subject experienced a DLT-defining event (Section 5.3). If the subject was infused with an inadequate number of BPX-701 T cells or could not complete scheduled evaluations (due to reasons other than toxicity) in the DLT evaluation period (e.g., disease progression, missed visits, non-compliance, subject withdrawal), the subject will be considered non-evaluable for DLT and will be replaced with a new subject. Evaluation of a cell dose level with at least 3 subjects completing the DLT evaluation period is required prior to determining the BPX-701 T cell dose for the next cohort. Dose escalation decisions for each Arm will be made independently. Therefore, more than one RDE may be defined (i.e., RDE-1 for Arm 1 and RDE-2 for Arm 2).

As of the date of this protocol amendment, Cohort 1 (Arm 1) is ongoing. Two subjects have been enrolled and received the BPX-701 infusion as planned (Table 2). No DLTs, SAEs, or treatment-related AEs have been reported. Neither subject has experienced a treatment-emergent adverse event necessitating rimiducid infusion. The inclusion of Arm 2 in the study design will proceed with approval of this amendment. Initiation of Arm 2 accrual expected thereafter; sequenced enrollment of an initial 3 uveal melanoma subjects into Cohort 1 (1.25 x 10^6 cells/kg) will be as described above.

Table 1: Dose Escalation/De-Escalation Enrollment Algorithm

Cohort[a, b]	If 0/3 subjects have DLT[c]	If 1/3 subjects have DLT	<1/6 subjects have DLT	>2 subjects have DLT
1	Expand to 6 evaluable subjects	Expand to 6 evaluable subjects	Declare RDE or expand by ≤6 subjects to confirm RDE	MTD exceeded; consider stopping rules (Section 5.6.2)
2	Expand to 6 evaluable subjects	Expand to 6 evaluable subjects	Declare RDE or expand by ≤6 subjects to confirm RDE	MTD exceeded; de-escalate to Cohort 1
3[d]	Escalate to Cohort 4	Expand to 6 evaluable subjects	Escalate to Cohort 4	MTD exceeded; de-escalate to Cohort 2
4	Escalate to Cohort 5	Expand to 6 evaluable subjects	Escalate to Cohort 5	MTD exceeded; no further enrollment at dose level
5	Expand to 6 evaluable subjects	Expand to 6 evaluable subjects	Declare RDE or expand by ≤6 subjects to confirm RDE	MTD exceeded; no further enrollment at dose level

DLT = dose limiting toxicity; MTD = maximum tolerated dose; RDE = recommended dose for expansion

a. Applicable to Arm 1 and Arm 2. Dose escalation decisions for each Arm will be made independently.
b. Refer to Table 2 for planned BPX-701 T cell dose levels assigned to each Cohort.
c. DLT evaluation period is Day 0 (BPX-701 T cell infusion) through Day 28.
d. Initial cohort for BPX-701 T cell dose escalations. For the first 3 subjects enrolled in Cohort 3, BPX-701 T cell infusions must be staggered by ≥28 days.

Table 2: Planned BPX-701 T Cell Dose Levels

Cohort	BPX-701 (PRAME TCR+) T cells
1	0.3×10^6 (±20%) cells/kg
2	0.625×10^6 (±20%) cells/kg
3 (Starting Dose)	**1.25×10^6 (±20%) cells/kg**
4	2.5×10^6 (±20%) cells/kg
5	5×10^6 (±20%) cells/kg

Maximum Tolerated Dose (MTD) is defined as the highest BPX-701 T cell dose level at which ≤33% subjects experience a DLT during the DLT evaluation period.

Maximum Administered Dose (MAD) is defined as the highest BPX-701 T cell dose administered in the event an MTD cannot be defined.

Recommended Dose for Expansion (RDE) is either identical to the MTD or MAD or a lower dose level of BPX-701 T cells selected on the basis of cumulative review of all available treatment-emergent data observed in Part 1 for Arms 1 and 2 independently. RDE will be represented by the dose of BPX-701 T cells administered that provides adequate BPX-701 T cell persistence and biological activity while not exceeding the MTD or MAD.

Additional subjects (up to 3) may be enrolled to a completed dose level that has previously been declared safe to better characterize safety and pharmacodynamic relationships. Intermediate dose levels between a non-tolerated dose level and a previous dose level determined to be safe may also be explored.

The total number of subjects enrolled in Part 1 will depend on the frequency of DLT and when RDE is determined for each Arm; however, it is estimated that approximately 12 to 18 subjects per Arm will be treated. Dose escalation in each Arm will proceed until the MTD is determined, or in the absence of an MTD, escalation will stop at the MAD (5.0×10^6 cells/kg).

5.4.2 Parts 2 and 3 (Phase 2): Dose Expansion

Parts 2 and 3 comprise a dose expansion phase designed to further safety, pharmacodynamics (including BPX-701 T cell persistence and response to rimiducid as applicable), and clinical activity of BPX-701 T cells administered at the RDE. Part 2 will begin once an RDE is determined in Part 1 (i.e., RDE-1 triggers Part 2 for Arm 1; RDE-2 triggers Part 2 for Arm 2). The opening of Part 3 is dependent upon antitumor activity observed in Part 2. Within each Arm, subjects will be monitored for clinical activity to enable early stopping for futility if sufficient antitumor activity is not demonstrated. For each Arm, the maximum planned enrollment in dose expansion is 40 subjects (Parts 2 and 3 combined).

- **Arm 1:** Up to 10 eligible subjects with relapsed AML and/or previously treated MDS will initially be enrolled (Part 2). If ≥2 subjects achieve complete or partial remission per ELN criteria or IWG criteria for AML and/or MDS, respectively, Part 3 may be opened to enroll up to an additional 30 subjects (Section 10.1).

- **Arm 2:** Up to 10 eligible subjects with metastatic uveal melanoma will initially be enrolled (Part 2). If one of the following are observed in Part 2, then Part 3 may be opened to enroll up to an additional 30 subjects (Section 10.1):

    - ≥1 complete or partial response as defined by RECIST v1.1; or,

    - ≥4 months median time to next treatment defined as the time from BPX-701 T cell infusion to initiation of next systemic therapy for the disease under study

5.5 Safety Review Committee

Subject safety will be monitored throughout all parts of the study by a Safety Review Committee (SRC) established by the sponsor, and will include representatives from Clinical Science, Safety Science/Pharmacovigilance, and Biostatistics. The SRC will meet at a regular frequency throughout execution of the clinical study to review all necessary cumulative data. In addition to safety and clinical assessments, a review of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities will be performed by the principal investigators and the study medical monitor. At each SRC review, appropriate recommendations will be made to the study team (e.g., continuation of the study as planned, study pause to

enrollment pending new safety evaluations, study discontinuation, specific indication or treatment arm/part closure, protocol modification/amendment). Decisions by the SRC will be made based on the totality of the available data. Ad-hoc SRC meetings may be called in addition to regularly scheduled meetings, as necessary, to provide recommendations on management of new or emerging safety concerns. Specific operational details of the SRC composition, frequency/timing of meetings, and member roles and responsibilities are detailed in the SRC charter.

5.6 Study Duration

Subjects will undergo routine safety monitoring and disease evaluations according to the schedule of assessments (Appendix 1) until disease progression is confirmed. At the time of confirmed progression or 12 months after the BPX-701 infusion, whichever comes first, subjects will complete an end of treatment (EOT) safety assessment. Thereafter, subjects will continue to be followed for long-term safety and vital status monitoring at least once annually for 15 years after the BPX-701 T cell infusion, death, the subject is lost to follow up, or consent is withdrawn, whichever occurs first.

5.6.1 End of Study

The end of the study is defined as the date when all subjects have completed the final protocol-specified safety assessment and/or discontinued study participation (withdrawal of consent or lost to follow-up), whichever occurs first.

The sponsor may terminate the study at any time for any reason. Should the study be terminated, subjects will be required to complete protocol-defined safety follow-up procedures.

5.6.2 Stopping Rules

The sponsor has the right to terminate the study at any time. Reasons for study termination may include but are not limited to incidence or severity of adverse events in this or other related studies which may indicate a potential hazard to subjects or unsatisfactory subject enrollment. The sponsor will notify the investigator if the sponsor decides to terminate the study.

Subjects will be monitored throughout the study for treatment emergent safety, DLTs and unacceptable toxicities (Section 5.3) by the SRC. The following safety stopping rules will be applied to mitigate potential risk to subjects:

- Grade 5 toxicity (death) due to any cause other than assessed as progressive disease by the investigator in ≥20% of all treated subjects (as defined in Section 10.2) within 28 days after the BPX-701 T cell infusion (i.e., Day 0 through Day 28)

- Grade ≥3 CRS, neurotoxicity, autoimmune, or other specific organ toxicity in ≥20% of all treated subjects (as defined in Section 10.2) unless clearly related to an alternative cause other than study treatment

5.7 Subject Enrollment, Registration, and Assignment to Treatment

Informed consent will be obtained from each subject after the nature of the study is explained and prior to the performance of any study-specific procedures. This study will utilize more than one informed consent form (ICF):

- Prescreening ICF: applies only to study assessments during the Prescreening period (Section 8 and Appendix 1). Consent for Prescreening assessments should be obtained from all potential subjects.

- Screening/Study Treatment ICF: applies to study assessments during the Screening, Treatment, and Posttreatment Follow Up periods (Section 8 and Appendix 1). The Screening/Study Treatment ICF is applicable only for subjects who satisfy all Prescreening requirements.

After signing the Screening/Study Treatment ICF, an eligibility determination based on the study inclusion/exclusion criteria (Section 6) will be conducted for each subject at a Screening Visit (Appendix 1). The investigator or designee shall complete a Subject Registration Form for eligible subjects and submit to the sponsor. The sponsor will provide the site with the planned treatment assignment (i.e., Arm, study Part, planned BPX-701 T cell dose level) and identification number for the subject. Subjects with assigned treatment will undergo apheresis according to the Schedule of Assessments (Appendix 1) and subsequently return to the site for a baseline evaluation and lymphodepletion within 1 week of the planned BPX-701 T cell infusion.

For this study, subjects who receive the BPX-701 T cell infusion are considered to be enrolled. Subjects that sign the Screening/Study Treatment ICF but do not receive BPX-701 T cells for any reason are considered to be screen failures. Furthermore, subjects that are determined to be PRAME-negative or have a positive result per infectious disease monitoring (Section 8.2.8 and Appendix 1) during the Prescreening period are also considered to be screen failures.

5.8 Subject Evaluability and Replacement

The criteria for subject evaluability and replacement for Part 1 is described in Section 5.4.1.

In Parts 2 and 3, subjects may be replaced when one of the following occurs:

- The subject is infused with a sub-optimal or an inadequate number of BPX-701 T cells that does not satisfy the RDE for the disease under study.

- The subject discontinues prior to the first planned on-study disease evaluation for reasons other than disease progression.

Any subject that meets the above replacement criteria must still be followed for treatment-emergent safety (Section 9.6) as well as long-term gene therapy monitoring (Section 8.4.6).

5.9 Study Completion

A subject will be considered to have completed the study if he or she has completed assessments up to and including the last protocol-specified visit or has experienced a clinical endpoint that precludes further continuation in the study (e.g., death).

5.10 Study Discontinuation/Withdrawal

Subjects are free to discontinue participation or withdraw consent from the study at any time, for any reason, and without prejudice to further treatment. Subjects who discontinue/withdraw from the study will receive treatment as deemed appropriate by the investigator and local standards of care. A subject will be withdrawn for the study for any of the following reasons:

- Lost to follow-up defined as documented, repeated failure after at least 3 attempts to contact the subject
- Withdrawal of consent
- Study termination by the sponsor or regulatory authority

When a subject is withdrawn prior to completing the study, the investigator will provide a reason for withdrawal.

A subject's participation in the study also may be discontinued at any time at the discretion of the investigator. The following may be justifiable reasons for the investigator to remove a subject from the study:

- The subject was erroneously included in the study
- The subject receives other investigational product(s) during the study
- The subject experiences an adverse event that is considered intolerable by the subject or the investigator

Data from discontinued/withdrawn subjects will be collected, stored and, whenever indicated, analyzed. These subjects will continue to be monitored for long-term safety (Section 8.4.6 and Section 9.6) and efficacy outcomes (Section 8.5 and Section 8.6) provided that the subject has not withdrawn consent for further follow-up.

6 SUBJECT ELIGIBILITY

Subject eligibility will be evaluated during the Prescreening and Screening periods of the study (Appendix 1). To undergo lymphodepletion and subsequent BPX-701 T cell infusion, subjects must satisfy inclusion/exclusion requirements at the Baseline visit (Appendix 1).

No waivers for study participation will be issued by the sponsor; subjects must meet all eligibility criteria as defined below.

6.1 Inclusion Criteria

1. Each subject (or their legally acceptable representative) must sign and date an informed consent form approved by the institutional review board/ethics committee, as appropriate, indicating that he/she understands the purpose of and procedures required for the study and are willing to comply. Consent is to be obtained prior to the performance of any study-specific procedures or tests that are not part of the standard of care for the subject's disease.

2. **Arm 1:**

   - MDS not responding to hypomethylation therapy or recurrence after initial response; or,
   - AML with disease relapse following first complete remission with intermediate or adverse genetics according to the ELN criteria (Dohner 2017)
     - Subjects with a prior treatment history of stem cell transplant must be >100 days post-transplant with no evidence of active GvHD and not requiring systemic immunomodulatory or immunosuppressive therapy defined as >10mg prednisone or equivalent per day and active use of a calcineurin inhibitor

   Arm 2:

   - Histologically or cytologically confirmed diagnosis of metastatic uveal melanoma
   - Measurable disease (at least one target lesion) per RECIST v1.1 (Eisenhauer 2009)
   - Adequate bone marrow function defined as:
     - Absolute neutrophil count ≥1,000/µL
     - Platelets ≥75,000/µL

3. HLA-A2.01 positive by local assessment

4. Documented positive myeloid blast or tumor expression of PRAME as determined by central testing of an available, representative bone marrow aspirate (fresh sample) or tissue specimen (formalin-fixed paraffin-embedded tissue, either from an archived sample or fresh biopsy) for Arm 1 and Arm 2, respectively

5. Absolute lymphocyte count ≥200/μL

6. Age ≥18 years

7. Life expectancy >12 weeks

8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Appendix 4)

9. Subjects must have adequate venous access for apheresis or agree to use of a central line for apheresis collection

10. Subject has adequate organ function:

    Cardiac: Left ventricular ejection fraction at rest must be ≥lower limit of institutional normal

    Coagulation: International normalized ratio ≤1.5

    Hepatic:

    - Direct bilirubin ≤2x upper limit of normal (ULN), or ≤3x if due to Gilbert's disease
    - Aspartate aminotransferase and alanine aminotransferase ≤3 x ULN, or ≤5 x ULN if liver metastases are present

    Renal: Creatinine ≤1.5 x ULN

11. Before planned BPX-701 T cell infusion, as well as during the study, a female subject must be either:

    - Not of childbearing potential defined as:

      (1) Premenarchal,

      (2) Postmenopausal (>45 years of age with amenorrhea ≥12 months),

      (3) Permanently sterilized,

      (4) Otherwise incapable of pregnancy; or,

    - Of childbearing potential and agrees to use 2 highly effective methods of birth control for at least 12 months after lymphodepletion

6.2 Exclusion Criteria

Subjects who meet any of the following criteria are NOT eligible for the study. Waivers are NOT permitted.

1. **Arm 1:**

   - Diagnosis of Acute Promyelocytic Leukemia
   - Primary refractory AML
   - Uncontrolled disseminated intravascular coagulation
   - Symptomatic or untreated central nervous system involvement by malignant cells
   - Peripheral blast count ≥20,000/μL

2. **Arm 2:**

   - Symptomatic, untreated or actively progressing central nervous system metastases. Subjects with prior brain metastases treated at least 2 weeks prior to the planned BPX-701 T cell infusion who are clinically stable and do not require chronic corticosteroid treatment are allowed
   - History of leptomeningeal disease

3. Ongoing toxicities related to prior anticancer therapy that have not resolved to Grade ≤1. Current unresolved Grade ≥2 non-hematologic toxicity may be allowed following discussion with and approval by the sponsor

4. Participation in any investigational drug study within 4 weeks prior to the planned BPX-701 T cell infusion

5. Chemotherapy (excluding hydroxyurea), targeted therapy, or radiotherapy (excluding palliative radiation) within 2 weeks, hydroxyurea within 1 week, or immunotherapy within 4 weeks prior to BPX-701 T cell infusion, other than salvage/lymphodepletion chemotherapy (Section 7.3 and Section 7.8)

6. Active autoimmune disease requiring immunosuppressive therapy. Subjects with vitiligo; type I diabetes; hypothyroidism, adrenal insufficiency, or hypophysitis only requiring hormone replacement; psoriasis not requiring systemic treatment or conditions not expected to recur; or history of Hashimoto's Thyroiditis on stable dose of thyroid hormone replacement therapy should not be excluded

7. Impaired cardiac function or clinically significant cardiac disease, including any of the following:

   - Symptomatic congestive heart failure requiring treatment;
   - Clinically significant cardiac arrhythmia;
   - Uncontrolled hypertension;
   - Acute myocardial infarction or unstable angina pectoris within 3 months prior to BPX-701 T cell infusion; or,
   - Marked limitation of physical activity due to symptoms, or unable to carry on any physical activity without discomfort (i.e., New York Heart Association Functional Class III-IV; Appendix 5)

8. Major surgical procedure, other than for diagnosis, within 4 weeks prior to BPX-701 T cell infusion, or anticipation of the need for a major surgical procedure during the study

9. Received a vaccine containing live virus within 4 weeks prior to the planned BPX-701 T cell infusion. Seasonal flu vaccines that do not contain live virus are permitted

10. Treatment with systemic chronic steroid therapy (prednisone >10mg daily or equivalent) within 7 days or 7 half-lives, whichever is shorter, prior to the planned apheresis date (See Appendix 6 on half-lives of common corticosteroids). Local steroid therapies (e.g., otic, ophthalmic, intra-articular or inhaled medications) are acceptable

11. Uncontrolled intercurrent illness including but not limited to poorly controlled hypertension or diabetes, or any medical condition determined by the investigator to be a risk for enrolling on the protocol

12. Uncontrolled infection requiring systemic therapy. Prior oral or IV antibiotics antifungals or antiviral medications must be discontinued at least 2 weeks prior to BPX-701 T cell infusion except for use of prophylactic antimicrobial agents

13. Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test during Screening. Subjects with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening are eligible for the study if HBV DNA test is negative. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed

14. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test during Screening. The HCV RNA test will be performed only for patients who have a positive HCV test

15. History of human immunodeficiency virus (HIV), or positive HIV test during Screening (unless not permitted by local regulations)

16. Subject is a woman of child-bearing potential is pregnant (positive serum β-human chorionic gonadotropin test at Baseline), planning to become pregnant within 12 months after lymphodepletion or is breastfeeding

17. Subject is a man who plans to father a child within 12 months after lymphodepletion

18. Known bovine product allergy

19. Malignant disease other than that being treated in this study. Exceptions to this exclusion are:

    - Malignancies that were treated curatively and have not recurred within 2 years prior to Screening
    - Completely resected basal cell and squamous cell skin cancers
    - Any malignancy considered to be indolent and that has never required therapy

7 STUDY TREATMENTS AND ADDITIONAL MEDICATIONS

7.1 Investigational Products

Refer to the Pharmacy Manual for details on the storage, preparation, and administration of BPX-701 T cells and rimiducid.

7.1.1 BPX-701 T Cells

BPX-701 is a genetically modified, autologous T cell product that incorporates a high affinity, HLA-A2.01-restricted PRAME-directed TCR and an inducible iCasp9 safety switch.

Manufacturing Process Description: BPX-701 is prepared from a patient's peripheral blood mononuclear cells (PBMCs), which are obtained via a standard apheresis procedure (Section 7.2). PBMCs are enriched for T cells which are then washed and expanded in cell culture. Once a target number of cells are available, the expanded T cells are transduced with a replication incompetent retroviral vector containing the PRAME TCR and rimiducid-inducible iCasp9 safety switch. The transduced T cells are formulated into a suspension, and cryopreserved. The final BPX-701 product must pass release testing, including a sterility test, before shipping as a frozen suspension in a patient-specific infusion bag(s). The estimated time from BPX-701 manufacture to release is approximately 2 to 4 weeks.

Packaging and Formulation: BPX-701 T cells are cryopreserved in 10-15 mL freezing medium (CryoStor, BioLife) and are stored frozen in cryostorage bags in the vapor phase of liquid nitrogen.

Labeling: The product label and insert for BPX-701 T cells contain the following information: lot number (which includes the subject ID number), BPX-701 T cell dose level, date of manufacture, storage conditions, sponsor, and product name. All products manufactured are also labeled with: "For Autologous Use Only" and "Caution: Limited by Federal Law to Investigational Use". The product will be labeled according to the requirement of each competent authority.

Shipping and Storage: Cryopreserved BPX-701 T cells will be shipped in the vapor phase of liquid nitrogen to clinical sites in a validated shipping container. BPX-701 T cells must be stored frozen in the vapor phase of liquid nitrogen (less than or equal to minus 150ºC) until the time of infusion.

7.1.2 Rimiducid for Injection

Rimiducid for Injection is a lipid-permeable analog of tacrolimus that functions as a dimerizing agent to induce clustering of engineered proteins containing the cognate dimerizer-binding domain.

Packaging and Formulation: Rimiducid for Injection is packaged in a 3 mL Type 1 clear glass serum vial. The contents of each vial are composed of the labeled content (10 mg in 2 mL) of rimiducid drug substance dissolved in a sterile, endotoxin free, 25% Solutol HS 15/Water for Injection solution at a rimiducid concentration of 5 mg/mL and at pH 5.0-7.5. Each vial is stoppered with a Teflon© coated serum stopper and a flip-off seal.

Labeling: The primary product label (applied directly to the vial) for the Rimiducid for Injection will contain the following information: product name, AP1903 (Rimiducid) Concentrate for Injection; the manufacturer's lot number; product concentration, 5 mg/mL; volume of solution available in the vial, 2 mL; total Rimiducid contents of the vial (10 mg); a statement, "For IV Infusion after Dilution" and the IND notation, "Caution: New Drug-Limited by Federal Law to Investigational Use". The product will be labeled according to the requirement of each competent authority.

Storage: Rimiducid for Injection vials must be stored at 5°C ± 3°C (41°F ± 5°F) in a limited access, qualified refrigerator, preferably without light.

7.2 Apheresis

After signing the Screening/Study Treatment ICF, subjects will undergo PBMC collection according to local institutional standards. To help mitigate the risk of insufficient sample collection due to treatment-related myelosuppression, the scheduled apheresis date should be at least 14 days or 5 half-lives, whichever is shorter, after the last dose of any prior or ongoing anticancer therapy. Prior to apheresis, hematologic parameters will be measured and recorded.

Results must demonstrate that the subject has adequate bone marrow function as follows. Use of transfusion and growth factor support is permitted in order to meet these criteria:

- Hemoglobin ≥8 g/dL
- Hematocrit ≥24%
- Platelets ≥20/µL
- Absolute lymphocyte count ≥200/µL

Using standardized continuous flow centrifugation, collect and process up to approximately 12-15 liters (goal range of 5 to 10 x 10^6 mononuclear cells) per institutional standard procedures. Record the volume processed and the duration of apheresis. A second day of collection is permitted. If the collection goal is not met after 2 collection days, the sponsor must be consulted immediately. During and after the apheresis procedure, subjects should undergo infectious disease monitoring per established regulatory guidelines. Evaluation prior to apheresis, venous access, monitoring and treatment of apheresis complications will be conducted according to institutional guidelines and must comply with federal, state, and the Foundation for the Accreditation of Cell Therapy regulations.

7.3 Lymphodepletion Prior to BPX-701 T Cell Infusion

Confirm availability of BPX-701 T cells prior to initiating the lymphodepletion regimen at the study site.

Refer to the Schedule of Assessments (Appendix 1) for safety assessments to be completed and recorded prior to initiation of lymphodepletion. Results must demonstrate that the subject meets institutional standards for lymphodepletion; conditioning chemotherapy should be withheld until resolution of clinically significant symptoms. If lymphodepletion is delayed in order to allow symptom management and recovery, the sponsor should be notified as soon as possible.

Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously on the fifth, fourth, and third day before infusion of BPX-701 T cells.

If the combination of cyclophosphamide and fludarabine is not tolerated, or if the investigator determines that combination-based lymphodepletion presents an unfavorable safety risk to a subject, then lymphodepletion should proceed with cyclophosphamide alone as per the aforementioned regimen following discussion with the sponsor.

7.4 BPX-701 T Cell Infusion

BPX-701 T cells are for autologous use only.

The Subject ID number must match the subject identifiers on the BPX-701 T cell infusion bag(s). Do not infuse BPX-701 T cells if the information on the subject-specific label does not match the intended patient.

BPX-701 T cells should be thawed and diluted as instructed in the Pharmacy Manual. BPX-701 T cells should be administered by IV infusion over 15-30 minutes using either central or peripheral venous access devices. The start and stop time of the infusion will be recorded.

BPX-701 T cells must be administered in an inpatient setting. Prior to administering BPX-701 T cells, subjects should receive premedication with acetaminophen and diphenhydramine per institutional standards for T cell products. Subjects will be observed for at least 4 hours after infusion and discharged once considered clinically stable. The expected inpatient stay is 1 night (i.e., admission on Day 0 with discharge on Day 1) unless unexpected toxicity occurs.

7.5 Rimiducid Infusion

Rimiducid drug substance is dissolved in a Solutol HS15 and therefore has the potential to induce an infusion or hypersensitivity reaction. To minimize or mitigate infusion-related toxicity, subjects should receive premedication with acetaminophen, diphenhydramine, ranitidine, and other supportive care therapy per institutional standards for potential anaphylaxis.

Rimiducid should be diluted with normal saline as described in the Pharmacy Manual. All subjects will receive IV rimiducid at a fixed dose of 0.4 mg/kg. Prior to administration, rimiducid should be diluted in normal saline to a volume that supports infusion over 2 hours. Rimiducid may be administered using either central or peripheral venous access devices. The start and stop time for the infusion will be recorded.

Rimiducid must be administered in an inpatient setting. Subjects will be observed for at least 4 hours after infusion and discharged once considered clinically stable. The minimum expected inpatient stay is 1 night, but the length of admission will depend on response to rimiducid and time to symptom resolution.

Rimiducid will be used in this study to mitigate uncontrolled toxicity induced by BPX-701. Therefore, rimiducid administration is limited to qualifying subjects who experience specific, treatment-related side effects in response to BPX-701 therapy. Refer to Section 7.6 for detailed criteria and guidelines for rimiducid infusion. Because rimiducid is designed to activate the iCasp9 safety switch, thereby initiating downstream signaling events to induce BPX-701 T cell apoptosis, **it is expected that any potential for further TCR-dependent anti-tumor activity will be significantly reduced or eliminated following rimiducid infusion**. Refer to Appendix 3 for the frequency and timing of pre- and post-infusion for research blood samples that must be collected from subjects who receive rimiducid.

7.6 Toxicity Management and Supportive Care Guidelines

All the guidelines within this section are general recommendations and investigators may use local institutional guidelines and clinical judgments in the management of toxicities and dose modifications.

7.6.1 Infusion Reactions / Hypersensitivity

BPX-701 is an autologous, fully humanized TCR therapy and is therefore less likely to be immunogenic and induce a hypersensitivity reaction. However, mild to severe infusion-related reactions have been previously reported with rimiducid (Rimiducid Investigator Brochure).

To minimize or mitigate infusion-related toxicity associated with BPX-701 and rimiducid, all subjects should receive premedication as described in Section 7.4 and Section 7.5, respectively. Additionally, the rate of infusion may be decreased and supportive care according to local standards may be used as needed. In case of infusion-related toxicity during the post-infusion observation period for BPX-701 T cells or rimiducid, subjects should receive symptom-directed supportive care (e.g., antihistamines, antipyretics, antiemetics as clinically indicated) as per institutional guidelines.

7.6.2 Management of T Cell-Related Toxicity

As BPX-701 is a type of adoptive T-cell therapy, adverse events similar to those observed with other engineered cell immunotherapies (e.g., chimeric antigen receptors, bispecific T-cell-engaging antibodies) may be reported. The two most commonly observed toxicities with T cell-based therapies are CRS and neurotoxicity (Lee 2014, Maude 2014, Brudno 2016, Hu 2016). Although these data are largely derived from clinical trials of CD19-targeted therapies for the treatment of hematologic malignancies, similar side effects have been reported in patients with non-hematologic cancers.

In vitro studies showed that T cells expressing the PRAME-specific BPX-701 TCR recognized a variety of tumor cell lines and primary AML blasts, positive for both PRAME and HLA-A2, as indicated by cytokine (i.e., interferon-γ) production (Amir 2011). Therefore, as part of the biological effect of BPX-701 may include cytokine modulation and as neurologic toxicity exists as a potential class effect for T-cell therapies, AEs of or related to CRS and neurotoxicity, respectively, may be anticipated.

Cytokine Release Syndrome

Clinical symptoms of CRS may include but are not limited to rigors, fever, nausea, chills, hypotension, hypoxia, and/or multiorgan toxicity. Symptoms may have acute onset either during or within minutes to hours after treatment administration and may coincide with peak cytokine levels (Kim 1993, Lee 2014). Alternately, symptoms may be delayed by a week or more following T cell infusion (Corrigan-Curay 2014). Subjects should be closely monitored during and after the BPX-701 T cell infusion for signs and symptoms indicative of CRS.

Grading criteria for CRS are provided in Table 3. Recommendations for the clinical management of CRS, **including when to administer rimiducid** (Section 7.5), are described in Table 4.

CRS is considered an adverse event of special interest for this study. Refer to Section 9.8 for reporting procedures.

Table 3: Grading Criteria for Cytokine Release Syndrome

Grade	Toxicity
Grade 1	Temperature ≥38°C and/or Grade 1[a] constitutional symptoms requiring symptomatic treatment only
Grade 2	Temperature ≥38°C and at least one of the following symptoms: • Oxygen requirement <40%; • Hypotension responsive to IV fluids or low dose of one vasopressor; or • Grade 2[a] organ toxicity
Grade 3	Temperature ≥38°C and at least one of the following symptoms: • Oxygen requirement ≥40%; • Hypotension requiring high-dose or multiple vasopressors[b]; or • Grade 3[a] organ toxicity or Grade 4 transaminitis
Grade 4	Temperature ≥38°C and at least one of the following symptoms: • Requirement for ventilator support; • Life-threatening hypotension; or, • Grade 4[a] organ toxicity (except Grade 4 transaminitis)

Adapted from Kim 1993, Lee 2014

a. Toxicity grade according to NCI CTCAE

b. High-dose vasopressors are defined as any of the following: noradrenaline ≥20 µg/min; dopamine ≥10 µg/kg/min; phenylephrine ≥200 µg/min; adrenaline ≥10 µg/min; if on vasopressin, vasopressin plus noradrenaline equivalent of ≥10 µg/min; and if on combination vasopressors (not including vasopressin), noradrenaline equivalent of ≥20 µg/min. The noradrenaline equivalent dose is calculated using the VASST trial vasopressor equivalent equation: [noradrenaline (µg/min)] + [dopamine (µg/kg/min)/2] + [adrenaline (µg/min)] + [phenylephrine (µg/min)/10] (Russell 2008).

Table 4: Recommendations for the Management of Cytokine Release Syndrome

Grade[a]	Sign/Symptom	Management[d]
Grade 1	Fever or organ toxicity	• Acetaminophen (or ibuprofen if not contraindicated) and hypothermia blanket for fever • Assess for infection using blood/urine cultures, chest radiography • Empiric broad-spectrum antibiotics and filgrastim, if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab 8 mg/kg[b] IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500-1000 mL normal saline (optional second bolus if SBP

Grade[a]	Sign/Symptom	Management[d]
		remains <90 mmHg) • If refractory to fluids, administer tocilizumab 8 mg/kg[b] IV or siltuximab 11 mg/kg IV (optional repeat tocilizumab after 6 hours as needed) • If refractory to fluids and anti-IL-6 therapy, administer vasopressors, consider transfer to ICU, obtain ECHO, and initiate other methods of hemodynamic monitoring as per institutional guidelines • If subject is high-risk[c] or if hypotension persists after 1-2 doses of anti-IL-6 therapy, consider dexamethasone 10 mg IV every 6 hours o *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours), rimiducid infusion as per Section 7.5* ***should be considered. The Bellicum medical monitor must be consulted prior to the decision to administer rimiducid.*** o *If administered, rimiducid may be used in conjunction with continued corticosteroids and anti-inflammatory agents. Samples for rimiducid PK analysis should be collected before and after rimiducid as described in Section 8.3.* o *If there is evidence improvement (e.g. partial response) but not complete resolution after the first dose of rimiducid, then repeat infusions may be given every 48 hours up to a total of 3 doses.* • Manage fever and constitutional symptoms as indicated for Grade 1
	Hypoxia	• Supplemental oxygen • Tocilizumab or siltuximab ± corticosteroids and other BSC as recommended for hypotension management o *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours), rimiducid infusion as recommended for hypotension management* ***should be considered***.
	Organ toxicity	• Symptomatic management of organ toxicities as per institutional guidelines • Tocilizumab or siltuximab ± corticosteroids and other BSC as recommended for hypotension management o *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours), rimiducid infusion as recommended for hypotension management* ***should be considered***.
Grade 3	Hypotension	• IV fluid boluses as needed, as indicated for Grade 2 • Tocilizumab and siltuximab as indicated for Grade 2, if not administered previously • Vasopressors as needed • Transfer to ICU, obtain ECHO, perform hemodynamic monitoring as for Grade 2 • Dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg IV every 6 hours o *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours),* ***administer rimiducid as per Section 7.5. The Bellicum medical monitor must be consulted prior to the rimiducid infusion.*** o *Rimiducid may be used in conjunction with continued corticosteroids and anti-inflammatory agents. Samples for rimiducid PK analysis should be collected before and after rimiducid as described in Section 8.3.*

Grade[a]	Sign/Symptom	Management[d]
		○ *If there is evidence improvement (e.g. partial response) but not complete resolution after the first dose of rimiducid, then repeat infusions may be given every 48 hours up to a total of 3 doses.* • Manage fever and constitutional symptoms as indicated for Grade 1
	Hypoxia	• Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab or siltuximab plus corticosteroids and other BSC as described above ○ *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours), **administer rimiducid** as recommended for hypotension management.*
	Organ toxicity	• Symptomatic management of organ toxicities as per institutional guidelines • Tocilizumab or siltuximab plus corticosteroids and other BSC as described above ○ *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours), **administer rimiducid** as recommended for hypotension management.*
Grade 4	Hypotension	• IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as indicated for Grade 3 • Methylprednisolone 1 g/day IV ○ *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours), **administer rimiducid** as recommended for hypotension management.* • Manage fever and constitutional symptoms as indicated for Grade 1
	Hypoxia	• Mechanical ventilation • Tocilizumab or siltuximab plus corticosteroids and other BSC as described above ○ *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours), **administer rimiducid** as recommended for hypotension management.*
	Organ toxicity	• As indicated for Grade 3

Adapted from Neelapu 2018

Abbreviations: ECHO=echocardiogram; ICU=intensive care unit; IV=intravenous; SBP=systolic blood pressure

a. Toxicity grade according to Table 3.

b. Maximum amount of tocilizumab per dose is 800mg.

c. High-risk subjects include those with bulky disease, comorbidities, and those who develop early onset CRS (≤3 days of BPX-701 T cell infusion).

d. If symptom management includes administration of rimiducid, refer to Section 7.6.4 for required safety blood samples for biomarker monitoring.

Neurotoxicity

Neurologic toxicity in response to T cell-based therapies encompasses a range of clinical symptoms including but not limited to diminished attention, language disturbance, impaired handwriting, confusion, disorientation, agitation, aphasia, somnolence, and tremors as well as seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure,

papilloedema, and cerebral edema (Neelapu 2018). Based on historical evidence with other cellular immunotherapies, neurologic symptoms may exhibit early onset (within days to a week) or may be delayed several weeks following treatment. Time to symptom resolution may be relatively short (hours to ~2-4 days) or prolonged for several weeks. Symptom severity may also fluctuate rapidly, necessitating close safety monitoring for signs and symptoms indicative of neurotoxicity.

Recommendations for the clinical management of neurotoxicity are described in Table 5.

Neurologic toxicity is considered an adverse event of special interest for this study. Refer to Section 9.8 for reporting procedures.

Table 5: Recommendations for the Management of Neurotoxicity

Grade[a]	Sign/Symptom	Management[c]
Grade 1	**Any**	• Symptomatic management as per institutional guidelines

Grade ≥2	**Focal[b]**	• Consider neurology consult and performing EEG
		• Perform daily neurological and mini-mental status examinations to evaluate for resolution/worsening of symptoms
		• Perform CNS imaging (MRI and/or contrast enhanced CT if MRI is not feasible or contraindicated)
		  ○ For persistent symptoms, consider repeat neuroimaging
		• Consider CSF evaluation for presence of cell counts (and differential), glucose, protein and gram stain for bacteria
		  ○ If negative for bacteria, consider CSF evaluations for other infectious etiologies (e.g., herpes viruses, JC virus, fungal, West Nile virus and toxoplasma)
		  ○ CSF samples should be sent to the sponsor for research use to evaluate for the presence of BPX-701 T cells
		• Administer anti-viral and/or anti-fungal therapy as per institutional standard of care should be considered if infectious etiology is suspected (tailored for lab data results)
		• Consider empiric use of anticonvulsants if seizure is expected
		• Start management of stroke/ischemia per institutional guidelines if suspected
		• A brain biopsy, as per the discretion of the site clinical research team, should be considered if other diagnostic tests do not reveal a reasonable etiology
		• For neurological symptoms without concurrent CRS or evidence of CNS/systemic infection, administer dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours
		  ○ Continue steroids until improvement to Grade 1 and then taper
		• If associated with concurrent CRS, administer tocilizumab 8 mg/kg[d] IV or siltuximab 11 mg/kg IV
		  ○ If refractory to anti-IL-6 therapy, administer dexamethasone or methylprednisolone as above
		  – *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours),* ***administer rimiducid*** *as per Section 7.5.*

Grade[a]	Sign/Symptom	Management[e]
		The Bellicum medical monitor must be consulted prior to the rimiducid infusion. – *Rimiducid may be used in conjunction with continued corticosteroids and anti-inflammatory agents. Samples for rimiducid PK analysis should be collected before and after rimiducid as described in Section 8.3.* – *If there is evidence improvement (e.g. partial response) but not complete resolution after the first dose of rimiducid, then repeat infusions may be given every 48 hours up to a total of 3 doses.* • Transfer to ICU with consideration of need for mechanical ventilation as clinically indicated
Grade ≥2	**Generalized[c]**	• Perform routine institutional care for subjects with altered mental status/obtundation (e.g., continuous vital sign monitoring, oxygen, suction, airway protection measurements and consideration of need for mechanical ventilation, ICU admission) • Neurology consult and EEG evaluation • Complete blood count analysis and peripheral blood smear to evaluate for thrombotic microangiopathy (TTP/HUS) • Evaluate for electrolyte and acid-base etiologies • Evaluate for liver dysfunction and evidence of hyperammonemia/veno-occlusive disease • Perform daily neurological and mini-mental status examinations to evaluate for resolution/worsening of symptoms • Perform CNS imaging (MRI and/or contrast enhanced CT if MRI is not feasible or contraindicated) o For persistent symptoms, consider repeat neuroimaging • Perform CSF evaluation for presence of cell counts (and differential), glucose, protein and gram stain for bacteria o If negative for bacteria, consider CSF evaluations for other infectious etiologies (e.g., herpes viruses, JC virus, fungal, West Nile virus and toxoplasma) o CSF samples should be sent to the sponsor for research use to evaluate for the presence of BPX-701 T cells • Consider empiric anti-viral and/or anti-fungal therapy as per institutional standard of care should be considered if infectious etiology is suspected (tailored for lab data results) • A brain biopsy, per the discretion of the site clinical research team, should be considered if other diagnostic tests do not reveal a reasonable etiology • For neurological symptoms without concurrent CRS or evidence of CNS/systemic infection, administer dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours o Continue steroids until improvement to Grade 1 and then taper • If associated with concurrent CRS, administer tocilizumab 8 mg/kg[d] IV or siltuximab 11 mg/kg IV o If refractory to anti-IL-6 therapy, administer dexamethasone or methylprednisolone as above – *If refractory to anti-IL-6 therapy and corticosteroids (i.e., no improvement after 48 hours),* ***administer rimiducid*** *as recommended above.*

Grade[a]	Sign/Symptom	Management[e]

Abbreviations: CNS=central nervous system; CRS=cytokine release syndrome; CSF=cerebral spinal fluid; CT=computed tomography; EEG=electroencephalogram; HUS=Hemolytic-uremic syndrome; ICU=intensive care unit; IV=intravenous; MRI=magnetic resonance imaging; SBP=systolic blood pressure; TTP=Thrombotic thrombocytopenic purpura

a. Toxicity grade according to NCI CTCAE.

b. Includes but is not limited to cranial nerve abnormalities, brachial plexopathy, ischemia, nystagmus, pyramidal tract syndrome, radiculitis, focal seizure, stroke, transient ischemic attack.

c. Includes but not limited to aphonia, ataxia, cognitive disturbance, depressed level of consciousness, dysarthria, dysphasia, encephalopathy, headache, hypersomnia, lethargy, memory impairment, meningismus, seizures, somnolence, tremor, visual disturbances.

d. Maximum amount of tocilizumab per dose is 800 mg.

e. If symptom management includes administration of rimiducid, refer to Section 7.6.4 for required safety blood samples for biomarker monitoring.

7.6.3 Autoimmune Toxicity

Autoimmune toxicity, so-called "on-target, off-tumor" toxicity results from antigen-specific attack on host tissues when the targeted tumor antigen is expressed on non-malignant tissues. The degree of on-target, off-tumor toxicity is likely related to the affinity of the TCR for its cognate antigen, the level of antigen expression on healthy tissue, the potency of the TCR, and the relative functional importance of the antigen as non-tumor target. PRAME is highly overexpressed a variety of malignancies, including those under investigation in this study (Epping 2006); whereas expression in normal tissues is primarily restricted to the testis, endometrium, ovary, and kidney epithelium (Ikeda 1997).

Safety Risk Assessment for On-Target, Off-Tumor Toxicity

At Baseline and at regular intervals following the BPX-701 T cell infusion, male subjects will be monitored for testicular health and function as described in Section 8.2.8 and Appendix 1. Similarly, male and female subjects will be offered the option to bank sperm and oocytes, respectively, for fertility preservation, as applicable, and if not already completed prior to Screening. All uveal melanoma subjects who have not undergone definitive enucleation at the primary disease site at Screening will undergo an ophthalmologic assessment as part of the physical exam prior to the BPX-701 T cell infusion. Subjects will be monitored following experimental treatment for signs and symptoms of uveitis and other ocular sequalae as described in Section 8.2.3 and Appendix 1. Renal function of all subjects will be assessed by repeat serum creatinine assessment as shown in Appendix 1.

If clinical signs or symptoms of anti-PRAME-directed autoimmune toxicity are suspected, subjects should receive symptom-directed supportive care as per institutional standards. If corticosteroid therapy is indicated, consider:

- Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours
    - If symptoms do not improve, consider an increased corticosteroid dose (e.g., dexamethasone 20 mg IV every 6 hours)

- Continue the corticosteroid regimen until symptoms improve to Grade 1 and then taper

For persistent symptoms that do not respond to corticosteroids (i.e., no improvement after 48 hours), administer rimiducid as per Section 7.5. The Bellicum medical monitor must be notified prior to the administration of rimiducid. Rimiducid may be administered in conjunction with continued corticosteroids and other supportive care medications. Samples for rimiducid PK analysis should be collected before and after rimiducid as described in Section 8.3. If there is evidence of improvement (e.g., partial response) but not complete response after the initial dose of rimiducid, then repeat infusions may be given every 48 hours up to 3 doses.

Autoimmune toxicity is considered an adverse event of special interest for this study. Refer to Section 9.8 for reporting procedures.

7.6.4 Safety Blood Samples for Biomarker Monitoring in response to CRS or Neurotoxicity

For subjects with signs or symptoms of CRS or neurotoxicity (Section 7.6.2), the following biomarker samples should be collected for safety monitoring at the time of the event or as soon as possible following diagnosis:

- Blood sample (serum) for peripheral cytokine assessment
- Whole blood sample for BPX-701 T cell tracking and functional activity

If event onset coincides with a planned time point (Appendix 1 and Appendix 2), proceed with the scheduled collection. Additional samples may be collected as clinically indicated for further safety monitoring. Refer to the Laboratory Manual for collection instructions.

7.6.5 Pharmacokinetics and Biomarker Blood Samples following Rimiducid Infusion

If rimiducid is indicated for symptomatic AE management (Section 7.6.2 and Section 7.6.3), the following blood samples should be collected for safety monitoring:

- Blood sample (serum) for peripheral cytokine assessment
- Whole blood sample for BPX-701 T cell tracking and functional activity
- Blood sample (plasma) for rimiducid pharmacokinetics

If more than one dose of rimiducid is administered, sample collection will be performed relative to the initial infusion only as detailed in Appendix 3. Samples may be collected more frequently as clinically indicated. Refer to the Laboratory Manual for collection instructions.

7.7 Concomitant Therapies

Subjects may receive concomitant medications and procedures as required or deemed necessary for supportive care, unless specifically restricted or prohibited in this study (Section 7.8).

During the study, subjects should continue the use of prescribed medications identified at baseline, consistent with study inclusion and exclusion criteria.

7.8 Prohibited Therapies

The following medications are not permitted from the Screening visit through completion of the EOT Visit unless otherwise indicated:

- Approved or investigational non-study chemotherapy, small molecule, immunotherapy, monoclonal antibody, radiotherapy (non-palliative), medical device or other cellular therapy intended to treat the disease under study unless there is clinical or radiographic evidence of confirmed disease progression.
    - Arm 1 only: if clinically indicated to control disease, salvage standard of care chemotherapy may be administered after apheresis and to up 2 weeks before the planned BPX-701 T cell infusion upon discussion with and approval by the sponsor.
    - Ongoing bisphosphonate therapy is allowed for supportive/palliative care.
    - Palliative radiotherapy (e.g., focused radiotherapy for bone metastases) may be permitted upon discussion with and approval by the sponsor.
- Systemic corticosteroids >10 mg/day of prednisone or equivalent (unless used for management of treatment-related toxicity)
- Live vaccines
- Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.
- Intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not permitted.

There are no prohibited therapies or procedures once the subject has completed the EOT visit.

8 STUDY PROCEDURES AND ASSESSMENTS

This study consists of an initial Prescreening phase, followed by a Screening phase, a Treatment phase (including an EOT visit), and a Posttreatment Follow Up phase.

Prescreening

All subjects must sign the Prescreening ICF prior to the conduct of any study-related prescreening procedures. The Prescreening phase will begin after applicable ICF signature when the first prescreening assessment is conducted. The includes a preliminary review of the study eligibility criteria (i.e., in anticipation of subsequent screening and study enrollment) and clinical evaluation as specified in the Schedule of Assessments (Appendix 1):

- HLA typing (if not part of prior medical records at the time of consent; Section 8.2.8)
- PRAME expression testing (fresh bone marrow aspirate or fresh/archived tumor tissue sample; Section 8.4.1)
- Infectious disease testing (blood sample for serology; Section 8.2.8)

Subjects who are HLA-A2.01 positive with documented PRAME tumor expression and blood test results that are negative or nonreactive for relevant communicable disease agents may proceed to the Screening phase. Subjects with alternate HLA typing, PRAME-negative disease, and/or evidence of active or ongoing infectious disease are not eligible for the study. The investigator should discuss with the subject alternate, non-protocol treatment options in accordance with local standards of care.

Screening

Prescreened subjects who are HLA-A2.01 positive with documented PRAME tumor expression and no evidence of relevant communicable disease must sign the Screening/Study Treatment ICF prior to conduct of any further study-related procedures. The Screening phase will begin after applicable ICF signature when the first screening assessment is conducted and includes a review of the eligibility criteria and clinical evaluation as specified in the Schedule of Assessments (Appendix 1). The following will be performed on eligible subjects up to 42 days before the planned BPX-701 T cell infusion:

- **Days -40 to -21:** apheresis procedure at the study site (Section 7.2) with subsequent BPX-701 T cell manufacturing from subject-derived T cells at the sponsor's manufacturing facility
- **Day -7 to Day -1:** baseline clinical assessments and lymphodepletion (Day -5 to Day -3; Section 7.3) prior to BPX-701 T cell infusion

The last result obtained prior to the BPX-701 T cell infusion will be used to determine eligibility to receive TCR therapy. Retesting of abnormal baseline values are allowed only once to reassess treatment eligibility.

Treatment

The Treatment phase begins on Day 0 with BPX-701 T cell infusion (Section 7.1.1). During the Treatment phase, subjects will be closely monitored for AEs, laboratory abnormalities, and antitumor response. The frequency of study site visits and required study procedures and assessments to be conducted during the Treatment phase are outlined in Appendix 1. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated.

An EOT visit will be scheduled 12 months after BPX-701 T cell infusion or at the time disease progression is confirmed or the subject is discontinued per investigator discretion (Section 5.10) unless the subject has died, is lost to follow-up, or has withdrawn consent for study participation. Assessments to be performed at the EOT visit are outlined in Appendix 1. The EOT visit should be completed before starting any subsequent anticancer treatment. If a subject is unable to return to the site for the EOT Visit, the subject should be contacted to collect information on any unresolved AEs.

Posttreatment Follow Up

After the EOT visit, subjects will enter the Posttreatment Follow Up phase and will complete routine follow-up visits for long-term safety evaluation and survival assessment (vital status and subsequent anticancer therapy monitoring) at least twice annually for 5 years and once annually from years 6 to 15 after BPX-701 T cell infusion. The frequency of study visits and required procedures to be conducted during the Posttreatment Follow Up phase are specified in Appendix 1.

- If the subject discontinued prior to disease progression, the results of disease assessments performed according to standard of care will be collected, if available. Efficacy evaluations should be performed until disease progression, the start of new anticancer therapy, death, withdrawal of consent, or the subject is lost to follow-up.

8.1 General Assessments

The following general assessments will be collected at Screening.

8.1.1 Demography

- Date of birth, age, gender, ethnicity, and race as allowed by local regulations

8.1.2 Medical History

- All active conditions, including the disease under study
    - For subjects with AML or MDS, the following disease characteristics will be collected:
        - Date of initial diagnosis

- Morphology (includes blast count and percentage in peripheral blood and bone marrow)
- Genetics (includes chromosomal abnormalities and gene arrangements)
- Molecular genetics and mutation profiling (if known)
- Immunophenotyping
- ELN risk category (for subjects with AML; Dohner 2017)
- Antecedent myeloid disorder (for subjects with AML)
- International Prognosis Scoring System category (for subjects with MDS; Greenberg 2012)

- For subjects with uveal melanoma, the following disease characteristics will be collected:
  - Date of initial diagnosis
  - Disease stage and histology and site(s) of disease
  - Molecular genetics and mutation profiling (if known)
  - Largest diameter of largest metastasis
  - Lactate dehydrogenase, alkaline phosphatase
  - Time from treatment of primary disease to development of metastatic disease

- Any past medical condition considered to be clinically significant by the investigator
- Height (without shoes)

8.1.3 Prior Anticancer Therapy

- All prior therapies, including surgery(ies), allogeneic hematopoietic stem cell transplants (AML and MDS only), radiation, and interventional treatment regimens for management of the disease under study, including start and stop dates and best response

8.2 Safety Assessments

Subject safety be assessed by collection of data on ECOG performance status, vital signs, weight, physical examination including ophthalmologic assessments, neurological evaluation and mini-mental status exam, cardiac function tests, AEs, concomitant medications, and routine clinical

laboratory assessments. Clinically significant changes from pre-treatment values in safety assessments should be reported as AEs. Safety assessments described below will be conducted according to Appendix 1. In addition to the weekly clinic visits scheduled during the first two months after the BPX-701 T cell infusion, mid-week phone calls may be made to the subject to help determine whether there is an emerging, acute condition that would require immediate safety evaluation by the investigator on an inpatient or outpatient basis.

8.2.1 ECOG Performance Status

The ECOG performance status scale (Appendix 4) will be used to grade changes in the subject's daily living activities.

8.2.2 Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature will be obtained at each indicated visit. On infusion days (BPX-701 and each dose of rimiducid, if applicable), collect prior to dosing (-60 to -5 min) and at 15 min, 30 min, 1 hr, 2 hr, and 4 hr (±5 min) after the start of the infusion and thereafter as clinically indicated until completion of the post-infusion safety monitoring period.

8.2.3 Physical Examination and Weight

Comprehensive Physical Examination

Complete physical examinations will be conducted at Screening and EOT. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver and spleen); extremities; and lymph nodes.

Uveal melanoma subjects who have not undergone definitive enucleation at the primary disease site will undergo a routine ophthalmic assessment according to institutional standards as part of the complete physical exam during Screening to establish a baseline for any treatment-emergent ocular toxicity.

Symptom-directed Physical Examination

Symptom-directed physical examinations may be conducted at all other visits as indicated. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

An ophthalmologist should be consulted if uveitis is suspected or any other signs and symptoms of eye-related inflammation including eye redness, eye pain, light sensitivity, blurred vision, floating spots in the field of vision, and decreased vision are observed in uveal melanoma subjects. Symptom-directed supportive care (e.g., slit lamp microscopy) should be performed as clinically indicated (Section 7.6.3).

Weight

Weight (kilograms) will be obtained at each indicated visit (prior to infusion, if applicable). The measurement obtained during Screening will be used in BPX-701 T cell manufacturing. The measurement obtained at Baseline will be used to calculate the appropriate dose of lymphodepletion therapy (Section 7.3). For qualifying subjects that receive rimiducid, the most recent measurement obtained prior to the infusion should be used in dose calculations.

8.2.4 Neurological Evaluation and Mini-Mental Status Exam

Subjects will undergo neurologic examination according to institutional standards at the frequency specified in Appendix 1. A mini-mental status examination (MMSE) should be performed in conjunction with all neurologic evaluations (Folstein 1975).

8.2.5 Cardiac Function Tests

Echocardiogram (ECHO)/Multi-gated Acquisition (MUGA) Scan

Routine ECHO/MUGA should be performed according to local standard practice. Cardiac function including left ventricular ejection fraction quantification should be assessed by the investigator for clinical significance and eligibility assessment.

Electrocardiogram (ECG) – applicable only for subjects that receive rimiducid

Routine 12-lead ECG should be performed according to local standard practice after the subject has rested in a recumbent or semi-recumbent position for ≥5 minutes. ECG parameters (e.g., heart rate, PR interval, QT interval, QRS duration, and corrected QT interval) should be interpreted by the investigator for clinical significance and eligibility assessment. Assessment frequency is defined in Appendix 3.

8.2.6 Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the Investigator as specified in Section 9.6.

8.2.7 Concomitant Medications

Medications used at the time of consent until the Baseline visit will be recorded as prior medications.

All concomitant medication administered from the Baseline visit until the EOT visit will be recorded (including the lymphodepletion regimen [Section 7.3], infusion premedication, and all over the counter medications, herbal remedies and dietary supplements). The generic name, dosage, duration, and reason for the concomitant medication should be included.

Following the EOT visit, concomitant medications will only be collected if associated with the management of an ongoing AE.

8.2.8 Clinical Laboratory Tests

Blood samples for clinical laboratory tests (Table 6) will be collected according to the frequency specified in Appendix 1. More frequent clinical laboratory tests may be performed if indicated by the overall clinical condition of the subject or by abnormalities that warrant more frequent monitoring. The investigator must review the laboratory reports, document this review, and ensure that any clinically relevant changes occurring during the study are recorded in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the **local** laboratory:

Table 6: Clinical Laboratory Tests

Hematology (eligibility and routine safety assessment)	
• White blood cell count with differential • Red blood cells • Hemoglobin	• Hematocrit • Platelets • Absolute neutrophil count
Chemistry (eligibility and routine safety assessment)	
• Sodium • Potassium • Chloride • Bicarbonate • Creatinine • Blood urea nitrogen • Glucose, non-fasting • Calcium • Magnesium	• Phosphate • Albumin • ALT • AST • Bilirubin • Direct bilirubin • Alkaline phosphatase • LDH • Uric acid
Coagulation (eligibility and routine safety assessment)	
• PT • PTT • INR	• Fibrinogen • D-Dimer
Urinalysis (screening only, as clinically indicated thereafter)	
Dipstick: • Specific gravity • pH • Protein • Glucose • Ketones • Blood	If dipstick is abnormal, microscopy will be used to measure sediment: • Red blood cells • White blood cells • Epithelial cells • Crystals • Casts • Bacteria
HLA-A Serotyping (prescreening for eligibility assessment)	
• HLA-A2.01	
Infectious Disease Panel (prescreening for eligibility assessment, collected ≤7 days of planned apheresis)	
• Anti-HIV-1 antibody • Anti-HIV-2 antibody • HIV viral load (if indicated) • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis B viral load (if indicated) • Hepatitis C antibody • Hepatitis C viral load (if indicated)	• Human T-lymphotropic Virus-1 antibody • Human T-lymphotropic Virus-2 antibody • Anti-Trypanosoma cruzi antibody • West Nile virus RNA • Syphilis • Cytomegalovirus antibody • Indirect antibody test (Coombs)
Pregnancy (eligibility and routine safety assessment for female subjects)	

• Serum (β-human chorionic gonadotropin [β-hCG] or urine pregnancy testing for women of childbearing potential	
Testicular Toxicity Monitoring (routine safety assessment for male subjects)	
• Testosterone • LH	• FSH • Inhibin B
Cytokines and CRP (routine safety assessment)	
• IFNγ • GM-CSF • TNFα	• IL-2 • IL-6 • CRP
Flow Cytometry (routine safety assessment)	
• CD3+Vβ1+ T cells to determine the number of transduced cells (absolute count and percent of total lymphocytes)	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRP=C-reactive protein; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; HLA=human leukocyte antigen; HTLV=human T-lymphotropic virus; GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN=interferon; IL=interleukin; INR=international normalized ratio; LDH=lactate dehydrogenase; LH=luteinizing hormone; PT=prothrombin time; PTT=partial thromboplastin time; TNF=tumor necrosis factor

8.3 Rimiducid Concentration Measurements (Pharmacokinetics)

Blood samples (plasma) for analysis of rimiducid concentrations will be obtained from qualifying subjects to characterize the PK profile of rimiducid. Samples will be collected at time points indicated in Appendix 3. If more than one dose of rimiducid is administered, PK sample collection will be performed relative to the initial infusion only. For all planned PK time points up to 8 hours post-infusion, blood must be collected from a peripheral vein contralateral to the arm/location into which rimiducid is administered. The time and date of each sample must be recorded; samples will be collected and processed by sites as outlined in the Laboratory Manual. All analyses will be conducted by the sponsor or designee.

8.4 Research Laboratory Assessments

Research laboratory assessments will be conducted to characterize the pharmacodynamics and mechanism of action of BPX-701 T cells as well as the effect of rimiducid, as applicable, on these parameters. The results may help to inform dose selection, characterize on-treatment immune responses and cancer progression, evaluate the efficacy of rimiducid as a safety switch, as well as monitor long-term safety. Research assessments planned for this study include:

- PRAME expression in bone marrow (fresh aspirate) from subjects with AML/MDS; or tumor tissue (archival or fresh biopsy) from subjects with uveal melanoma as determined by quantitative polymerase chain reaction (qPCR)
- T-cell phenotyping and functional activity (transduced and non-transduced) using standard markers via flow cytometry analysis of whole blood and PBMCs
- Persistence of peripheral BPX-701 T cells by qPCR (vector copy analysis) and flow cytometry (cell counts)
- Serum cytokine analysis using a multiplex analysis technique

- Gene expression changes in peripheral blood or bone marrow (AML/MDS) or the tumor microenvironment (uveal melanoma)

- Bone marrow or tumor microenvironment assessment of markers associated with immune infiltrate including BPX-701 T cells for AML/MDS or uveal melanoma, respectively

- Gene therapy monitoring for vector and replication competent retrovirus (RCR)

Peripheral blood and tumor (bone marrow biopsy/aspirate or tissue biopsy as appropriate for the disease under study) samples will be collected at the visits and time points indicated in Appendix 1 and further detailed in Appendix 2. Detailed information regarding sample collection, processing, and shipment is outlined in the Laboratory Manual.

All analyses will be conducted by the sponsor or designee. Blood samples, bone marrow biopsies/aspirates, tumor tissue biopsies, and available archival tumor tissue may also be used for exploratory evaluation of DNA, RNA, and/or proteins as potential tumor and immune-associated biomarkers.

Based on emerging data, site-specific collection feasibility, or for other operational reasons, the timing for sample collection may be adjusted, or certain samples may not be collected. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data and/or analyzed. No pharmacogenomic analyses will be conducted on the biomarkers samples.

8.4.1 PRAME Evaluation

A requirement for trial inclusion is documented positive myeloid blast or solid tumor expression of PRAME, as appropriate for the disease under study, as determined by central qPCR assessment of an available bone marrow aspirate or tumor tissue biopsy. For subjects with AML or MDS, a fresh bone marrow aspirate will be collected during the Prescreening phase for PRAME testing (Appendix 1). For subjects with uveal melanoma, PRAME expression will be evaluated using formalin-fixed, paraffin embedded (FFPE) tumor tissue. During the Prescreening phase, all potential uveal melanoma subjects will be required to provide archived tumor tissue (FFPE block, preferred, or scrolls) or to undergo tumor biopsy if an archived sample is not available (Appendix 1). From the time of sample receipt by the central analysis vendor, it is anticipated that PRAME expression results should be available within 7 to 14 days.

8.4.2 BPX-701 T cell Tracking and Functional Activity

Persistence of genetically modified BPX-701 T cells in PBMCs isolated from whole blood will be assessed by flow cytometry (e.g., absolute count of CD3+Vβ1+ T cells and percentage within the total lymphocyte population) and qPCR. Flow cytometry using standard activation markers may

also be used for immunophenotyping of both BPX-701-engineered and patient-derived T cells. In addition, T cell functional activity may be analyzed in PBMC samples using appropriate techniques such as intracellular cytokine staining or a PRAME-specific cytotoxicity assay, if sufficient material is available for testing.

8.4.3 Cytokines

In addition to local serum testing for time-sensitive routine safety monitoring (Table 6), blood (serum) will also be collected for centralized pharmacodynamic assessment using a multiplexed cytokine assay that includes evaluation of IFNγ, GM-CSF, TNFα, IL-2, and IL-6.

8.4.4 Immunogenicity Assessment

Based on emerging data, residual blood (serum) samples collected for centralized cytokine assessment (Section 8.4.3) may be explored for the presence of anti-BPX-701 antibodies. Anti-BPX-701 antibodies will be assessed using a validated method.

8.4.5 Pretreatment and On-Treatment Tumor Sampling

AML or MDS

Subjects with AML and MDS will undergo repeat bone marrow aspirate and peripheral blood sampling prior to as well as after BPX-701 T cell infusion as part of routine disease evaluations to determine response to treatment (Appendix 1).

Uveal Melanoma

Subjects with uveal melanoma are required to provide a pretreatment (tissue collected at Baseline) as well as on-treatment, fresh tumor biopsy following BPX-701 T cell therapy (tissue sample collected between Days 14 and 21; Appendix 1).

The investigator should select a representative lesion amenable to post-infusion fresh biopsy. The biopsy should be obtained from appropriate tumor site(s) using standard techniques to yield adequate tissue for analysis. Fine needle aspirations will not be acceptable. A second post-treatment biopsy may also be collected from all subjects at the time of disease progression, provided the lesion for biopsy is accessible and tissue collection is clinically feasible.

8.4.6 Gene Therapy Monitoring

Per FDA guidelines, subjects will undergo blood testing for vector and RCR prior to BPX-701 T cell infusion and then every 6 months from the date of infusion (i.e., Day 0) for 5 years (Table 7). Beginning with year 6, blood samples will be drawn annually for another 10 years (total of 15-year follow-up). All samples collected at pre-infusion and during the initial 12 months after BPX-701 T cell therapy will be analyzed for RCR. If a result is positive during this time, all remaining samples for that subject collected during the 15-year follow up period will also be analyzed. If all results are negative during the initial 12 months of RCR testing, samples will

continue to be collected but will be centrally archived by the sponsor or designee for analysis at a future date.

Table 7: Gene Therapy Monitoring Schedule

Time Point of Collection	Clinical Evaluation	Blood
Prior to lymphodepletion	X[b]	X
Month 3[a]	X[b]	X
Month 6[a]	X[b]	X
Month 12[a]	X[b]	X
Every 6 Months up to Year 5[a]	X[c]	X[d]
Every 12 Months up to Year 15[a]	X[c]	X[d]

a. After the BPX-701 T cell infusion
b. Includes ECOG performance status, vital signs, symptom-directed physical exam, and adverse event monitoring. Refer to Appendix 1.
c. Includes adverse event monitoring.
d. If blood samples collected during the initial 12 months after BPX-701 T cell infusion are negative, remaining blood samples collected will be archived.

8.5 Efficacy Assessments for Subjects with AML or MDS

Disease evaluation will include clinical examination, routine peripheral blood and bone marrow sampling (aspirate or biopsy), and appropriate radiographic imaging techniques. The latter should be used to characterize known or suspected extramedullary disease sites. CNS imaging is required at Baseline for subjects with associated clinical signs or symptoms; if positive, a confirmatory lumbar puncture should be performed. Subjects without extramedullary or CNS disease do not require on-study body or brain imaging, respectively, unless clinically indicated.

Refer to Appendix 1 for detailed information regarding the schedule and frequency for peripheral blood and bone marrow sampling. Samples may be collected more frequently if clinically indicated. If a subject discontinues the study for reasons other than progression or relapse, continue marrow assessments per standard of care frequency until documented progression/relapse, withdrawal, or study end.

Response assessment will be determined locally by the investigator using ELN criteria for AML (Appendix 9) or IWG criteria for MDS (Appendix 10).

8.6 Efficacy Assessments for Subjects with Uveal Melanoma

Radiographic tumor evaluation will include clinical examination and appropriate imaging techniques, preferably computed tomography (CT) scans with contrast of the chest, abdomen, and pelvis with ≤5 mm slice thickness. Magnetic resonance imaging (MRI) is required at Baseline to document known or suspected liver as well as CNS metastases. Subjects without brain lesions do not require brain imaging on study unless clinically indicated. A bone scan should be conducted for known or suspected bone metastases.

If CT scan is contraindicated (e.g. allergy to contrast dye), MRI should be performed. Tumor

imaging will be performed using the same assessment technique throughout the study. Refer to Appendix 1 for detailed information regarding the schedule and frequency for tumor imaging. If a subject discontinues study treatment for reasons other than progressive disease, continue imaging per standard of care frequency until documented disease progression, withdrawal, or study end.

Radiographic imaging will be evaluated locally by the investigator for response assessment using RECIST v1.1 (Appendix 7). The investigator/local radiology review will also use irRC (Appendix 8) to assess tumor response and progression and make treatment decisions.

If an initial complete response (CR) or partial response (PR) is noted, confirmatory scans must be performed at least 4 weeks later. In the case of stable disease (SD), follow-up imaging must have met the SD criteria at least once after study entry and no less than 4 weeks.

If radiographic disease progression is observed, another scan should be performed no less than 4 weeks later to confirm disease progression prior to treatment discontinuation. Subjects discontinued after confirmation of progression should complete the EOT Visit and enter the Posttreatment Follow-Up Period.

9 ADVERSE EVENT REPORTING

9.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry variables vital signs and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The sponsor or its designee is responsible for reporting relevant SAEs to the FDA, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive, and/or local regulatory requirements.

9.2 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

1. AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period

2. Pre-existing medical conditions judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

Abnormal laboratory values or test results that induce clinical signs or symptoms and are considered clinically significant.

9.3 Serious Adverse Events (SAE)

An SAE is any AE that is any of the following:

1. Fatal (i.e., the AE actually causes or leads to death)
2. Life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death)
3. Requires or prolongs in subject hospitalization
4. Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
5. A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
6. Considered a significant medical event by the investigator (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

The investigator is responsible for ensuring that all AEs and SAEs are recorded on the CRF and reported to the sponsor in accordance with protocol instructions.

9.4 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and the potential relationship (causality) between the AE and the study treatment.

9.4.1 Assessment of Severity

The severity of all AEs except CRS will be graded according to the NCI CTCAE v. 4.03 (http://ctep.cancer.gov/reporting/ctc.html). Grading criteria for CRS are provided in Table 3. For AEs not listed in the CTCAE, the following grading system will be used:

- Mild (CTCAE Grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (CTCAE Grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental activities of daily living
- Severe (CTCAE Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Life-threatening (CTCAE Grade 4): Life-threatening consequences; urgent intervention indicated
- Death (CTCAE Grade 5): Death related to AE

9.4.2 Assessment of Causality

The Investigator will estimate the relationship between the study treatment (BPX-701 T cells, rimiducid, or both) and the occurrence of each AE or SAE. The relationship (synonym: causality) is based on the Investigator's clinical judgment regarding the likelihood that the event may (certainly, probably, possibly) or may not be (unlikely, unrelated) attributed to the study treatment.

9.5 Disease-Related Events Not Qualifying as AEs

An event which is part of the natural course of the disease under study (i.e., disease progression, death due to disease progression) should not be recorded as an AE or serious AE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the definition of an AE or SAE (Section 9.2 and Section 9.3).

For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE or SAE as applicable.

9.6 Adverse Event Reporting Period

Safety reporting periods for this study are defined in Table 8.

Table 8: Safety Reporting Periods

Event Type	Reporting Period	Additional Requirements
SAEs (screening)	Date of informed consent and prior to BPX-701 infusion	• Report new SAE only if caused by a protocol-mandated intervention during Screening
AEs (treatment-emergent)	No less than 30 days following infusion of BPX-701 or the last dose of rimiducid, as applicable, whichever occurs later	• Report new AEs for up to 15 years if assessed as related to BPX-701 or rimiducid
SAEs (treatment-emergent)	No less than 180 days following infusion of BPX-701 or the last dose of rimiducid, as applicable, whichever occurs later	• Report new SAEs for up to 15 years if assessed as related to BPX-701 or rimiducid • Report diagnosis of any new secondary malignancy regardless of relationship to study treatment for up to 15 years
Adverse events of special interest (treatment-emergent)	No less than 180 days following infusion of BPX-701 or the last dose of rimiducid, as applicable, whichever occurs later	• Report new AESI for up to 15 years if assessed as related to BPX-701 or rimiducid
Pregnancy of subjects or partner	No less than 12 months following the last dose of cyclophosphamide in the lymphodepletion regimen	• As per Section 9.10 • Report diagnosis of any congenital abnormality in offspring from a study participant for up to 15 years

9.7 Reporting Requirements for SAEs

9.7.1 Initial Reports

An SAE report will be completed for each observed SAE. The Investigator will submit SAE information to the sponsor or designee within 24 hours of learning about the initial event. The initial report will contain all available details about the event. If the Investigator does not have all information about an SAE within the submission window, the Investigator will not wait to receive additional details before notifying the sponsor of the event. Relevant follow-up information should be submitted to the sponsor or designee within 24 hours of awareness of the new information and/or upon request.

9.7.2 Expedited Reporting Requirements

The sponsor or designee will report all events qualifying as Suspected Unexpected Serious Adverse Reactions (SUSARs) to the relevant health and regulatory authorities and Investigators in the form of an expedited safety report. SUSARs will be submitted as follows:

- Within 7* calendar days for unexpected life-threatening or fatal SAEs that are unexpected and considered related to study treatment
- Within 15* calendar days for all other SAEs that are unexpected and considered related to study treatment

*Note: These timeframes begin with the first notification of the SUSAR from the investigator to the sponsor or designee.

In addition to safety reporting requirements of the sponsor, the investigator must also comply with all applicable requirements related to the reporting of SAEs to local health and regulatory authorities.

9.8 Adverse Events of Special Interest

The following events are considered adverse events of special interest (AESI) and should be reported following SAE reporting procedures (Section 9.7). These events have been identified as serious risks associated with approved T-cell-based therapies and can result in severe and fatal reactions. The following AEs (irrespective of severity, attribution, or seriousness) will therefore be monitored as AESI in this study:

- Cytokine release syndrome
- Neurologic toxicity
- Autoimmune toxicity
- Any event that satisfies the definition of DLT (Section 5.3)
- Any event (other than the above) for which rimiducid is administered as supportive care

9.9 Adverse Event Follow-Up Reporting

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized (in the case of persistent impairment), the subject dies or is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the case report form and in the subject's medical record to facilitate source data verification (SDV).

For SAEs, the sponsor or designee may utilize telephone, fax, or electronic mail communications as well as monitoring visits to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report). Within 24 hours of receipt of new follow-up information, the Investigator must update the SAE report and submit any supporting documentation to the sponsor or designee.

9.10 Pregnancy Reporting

The investigator should report to the sponsor or designee all instances of pregnancy in female subjects or partners of male subjects within 24 hours of their knowledge of the pregnancy using the Pregnancy Form. In addition, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be

reported using the SAE Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9.11 Safety Reporting Contact Information

SAE and pregnancy reporting contact information are provided below. All reports (initial and follow-up) for screening and treatment-emergent SAEs, AESI, and pregnancy should be directed to the electronic SAE reporting mailbox (primary route of submission) or facsimile (back-up):

Email: [redacted]

Fax (back-up): [redacted]

Sites should contact the sponsor medical monitor for any safety concerns or questions.

Primary Medical Monitor:	[redacted]
Email:	[redacted]
Telephone No (direct):	[redacted]
Alternate Telephone No (mobile):	[redacted]
Back-up Medical Monitor:	[redacted]
Email:	[redacted]
Telephone No (direct):	[redacted]
Alternate Telephone No (mobile):	[redacted]

10 STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics by dose level/Part and tumor type (i.e., Arm 1 reported separately from Arm 2). Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Descriptive summaries of time to event data from Kaplan Meier estimates will include the number of events, number censored, medians, quartiles and 95% confidence intervals. Graphical summaries of the data may be presented. All data will be listed for all subjects.

The sponsor will establish a clinical data cutoff date for clinical study report analysis reporting 12 months after the last subject has received BPX-701 or after all subjects have discontinued the study, whichever comes first.

10.1 Sample Size Determination

Part 1 (Phase 1): Cell Dose Escalation

One or more dose cohorts of 3 to 6 subjects will be enrolled at a cell dose level including at least 6 subjects at the RDE. The total number of subjects enrolled in Part 1 will depend on the frequency of DLT and when RDE is determined for each disease indication.

Parts 2 and 3 (Phase 2): Dose Expansion

The dose expansion phase of this study is not designed to make explicit power and Type I error considerations for a hypothesis test. Instead, it is designed to obtain preliminary efficacy and additional safety and PK/PD data on the PRAME-TCR therapy, BPX-701, administered at the respective RDE to subjects with either AML/MDS or uveal melanoma that express sufficient levels of PRAME. Preliminary efficacy will be assessed as follows:

- **For AML and MDS combined:** the proportion of AML subjects with complete* or partial remission per ELN criteria pooled together with the proportion of MDS subjects with complete* or partial remission per IWG criteria during Part 2 as well as Part 3 (provided a minimum, cumulative 20% remission rate is observed in Part 2 and that the sponsor deems as having a promising risk/benefit profile)

  *Note: Complete remission includes CR_{MRD-}, CR, and CR_i (for AML) and CR and CR marrow (for MDS)

- **For uveal melanoma:** the proportion of subjects with an objective response (CR or PR) per RECIST v1.1 during Part 2 as well as Part 3 (provided a minimum 10% ORR is observed in Part 2 and that the sponsor deems as having a promising risk/benefit profile)

Given the exploratory nature of this study, it is anticipated that at least one interim analysis per arm will be conducted during the dose expansion phase when 10 patients have been enrolled and completed at least one post-baseline disease evaluation (Part 2). A posterior probability will be used to guide further enrollment based on observed clinical activity in each disease indication compared to historical control response rates (i.e., ≤20% for AML/MDS; ≤10% for uveal melanoma). If the interim analysis suggests that the clinical activity in an experimental arm is higher than that observed in historical reports, up to 30 additional subjects may be enrolled for a total of 40 subjects (Parts 2 and 3 combined). Accrual of up to 30 additional uveal melanoma subjects may also proceed if the median time to next treatment (defined as the time from BPX-701 T cell infusion to initiation of next systemic therapy for the disease under study) observed in the initial 10 subjects is ≥4 months.

If the remission rate is ≤10% for the first AML/MDS subjects in both Parts 2 and 3 (at least 20 subjects), further enrollment in Part 3 will be stopped. Similarly, if the disease control rate, defined as the proportion of uveal melanoma subjects with an objective response (CR or PR) or stable disease per RECIST v1.1 is <15% for the first subjects in both Parts 2 and 3 (at least 10-15 subjects), further enrollment in Part 3 will be stopped. Interim analyses will be performed and interpreted by the sponsor.

10.2 Analysis Sets

The following analysis sets will be used for this study. Each analysis set will be applied to Arm 1 and Arm 2.

All treated: all subjects with AML or MDS who were infused with any quantity of BPX-701 T cells (this is the safety population)

Intent-to-treat (ITT): all subjects who were infused with the planned dose of BPX-701 T cells

Efficacy*:* all ITT subjects in Parts 2 and 3 with at least one evaluable post-baseline tumor response assessment

DLT evaluable: all ITT subjects in Part 1 who complete through Day 28 or who had a DLT during the DLT evaluation period

PK*:* all ITT subjects with at least 1 evaluable concentration measurement of rimiducid

10.3 Subject Disposition

Subject disposition summaries will include the number of enrolled subjects, the number of subjects receiving BPX-701 T cells, the number of subjects receiving rimiducid, the number of subjects completing the study, the number of subjects withdrawing prematurely, and the reasons for study discontinuation.

Demographics, baseline disease characteristics, prior disease related therapies, and concomitant medications will be summarized using descriptive statistics.

10.4 Safety Analyses

All safety analyses will be performed on data from the all treated analysis sets (Arm 1 and Arm 2 separately) according to BPX-701 T cell dose level. The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, BPX-701 T cell infusion. The safety parameters to be evaluated are the incidence, severity, and type of AEs, clinically significant changes in the subject's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to study treatment and reasons for discontinuation will be tabulated.

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and assessed for severity by the investigator using the NCI CTCAE v4.03. AEs will be summarized by system organ class and preferred term and presented in decreasing order of frequency. Incidences of AEs and SAEs will be summarized overall and with respect to CTCAE grade and relationship to study drug. AEs leading to treatment discontinuation, infusion interruption, and with an outcome of death will also be summarized. Incidences of SAEs and AESIs will be summarized overall and with respect to relationship to study treatment.

Clinically significant changes from baseline in ECOG and changes from baseline in CTCAE grading for vital signs and safety laboratory parameters will be examined and presented in shift tables. All abnormal laboratory parameters will be listed.

10.5 Pharmacokinetic Analyses

Pharmacokinetic analyses will be described separately outside the context of this protocol and in the SAP.

10.6 Efficacy Variables and Analyses

Clinical response to study treatment will be determined by the investigator's assessment.

For **AML and MDS**, all efficacy endpoints will be defined and analyzed according to the ELN or IWG criteria, respectively (Dohner 2017; Cheson 2006). The following efficacy endpoints will be derived and summarized descriptively according to study Part and BPX-701 T cell dose level:

Remission Rate is defined as the combined portion of AML subjects with CR_{MRD-}, CR, CR_i, or PR plus MDS subjects with CR or marrow CR

Morphologic leukemic-free state (MLFS) defined as the proportion of AML subjects with bone marrow blasts <5%, absence of blasts with Auer rods, and no extramedullary disease but with no hematologic recovery

Time to next treatment is defined as the date of BPX-701 T cell infusion to the initiation of next systemic therapy for the disease under study.

Relapse-free survival (RFS) is measured from the date of achievement of a remission (as defined above) until the date of relapse or death from any cause. Subjects who do not experience disease relapse and are alive will be censored at the time of last evaluable tumor assessment.

Event-free survival (EFS) subjects measured from the date of BPX-701 T cell infusion to the date of primary refractory disease, disease relapse following remission (as defined above), or death from any cause. Subjects who do not experience disease progression or relapse and are alive will be censored at the time of last evaluable tumor assessment.

Overall survival (OS) subjects measured from the date of BPX-701 T cell infusion to the date of death from any cause. Subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive.

For **uveal melanoma**, all efficacy endpoints will be defined and analyzed according to RECIST v1.1 (Eisenhauer 2009) and irRC (secondary evaluation; Wolchok 2009). The following efficacy endpoints will be derived and summarized descriptively according to study Part and BPX-701 T cell dose level:

Objective Response Rate (ORR) is defined as the proportion of subjects with a best overall response of partial response (PR) or complete response (CR).

Duration of response (DOR) is defined as the date from the first tumor assessment that supports the subject's objective disease response to the date of disease progression or death due to any cause.

Disease control rate (DCR) is defined as subjects with CR, PR, or stable disease (SD).

Time to next treatment is defined as the date of BPX-701 T cell infusion to the initiation of next systemic therapy for the disease under study.

Progression-free survival (PFS) is defined as the date of BPX-701 T cell infusion to the first documentation of disease progression or death due to any cause. Subjects who do not experience progressive disease and are alive will be censored at the time of last evaluable tumor assessment.

OS defined as the date of BPX-701 T cell infusion until date of death due to any cause. Subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive.

10.7 Research Laboratory Analyses

Analyses of research laboratory samples, tumor markers, samples for gene therapy monitoring, tumor biopsies, and immune response data will be described separately outside the context of this protocol and in the SAP.

10.8 Interim Analysis

For each dose expansion arm (Arm 1 and Arm 2 separately), one interim analysis is planned to evaluate the clinical activity of BPX-701 T cells. The analysis will be performed after approximately 10 subjects have been enrolled and have at least 1 post-baseline disease assessment. The interim analysis will follow the rules outlined in Section 5.4.2. Review and communication of results will be addressed by the SRC as described in Section 5.5.

10.1. Data Monitoring Committee

There will be no formal Data Monitoring Committee for this study. Treatment emergent safety and efficacy data will be reviewed by the SRC comprised of participating investigators in the study, the medical monitor, and sponsor representatives (Section 5.5).

11 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1 Institutional and Ethical Review

The study will be conducted according to the ethical principles of the declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/120/EG), FDA and other international regulatory agencies.

11.2 Investigator Responsibilities

By signing this document, the investigator agrees to carry out this research in accordance with the protocol approved by the IRB/EC, ICH GCP and all applicable regulatory requirements. The investigator is responsible for ensuring that site personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

11.3 Subject Informed Consent and Human Subject Protection

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to initiation of any study-related procedures.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be approved by all applicable local regulatory authorities and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. As part of this discussion, the investigator should clarity alternate therapy options and the associated risks/benefits.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.4 Confidentiality and Privacy

Participant confidentiality and privacy is held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or EC, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Subject research data, which is for purposes of statistical analysis and scientific reporting, will be entered into an electronic clinical study database maintained by the sponsor or designee. This will not include the subject's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived according to the sponsor's standard policies.

11.5 Clinical Monitoring

Clinical site monitoring will be conducted by the sponsor or designee to ensure that the rights and well-being of trial participants 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/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The investigational site will provide direct access to all trial-related information, source data/documents, and reports for the purpose of monitoring by the sponsor, and inspection by local and national regulatory authorities.

11.6 Data Handling and Record Keeping

11.6.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility,

and timeliness of the data reported. The investigator will review all the case report forms for each subject and confirm the completeness, medical correctness, and plausibility of the documented data by his/her electronic signature.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Study data will be entered by the site staff into a 21 CFR Part 11-compliant electronic data capture system maintained by the sponsor or designee. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly into the electronic CRF from the source documents and should be consistent with the latter.

11.6.2 Study Records Retention

Study documents should be retained by the site for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the reviewing IRB/EC per local regulations.

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13 APPENDICES

13.1 Appendix 1: Schedule of Assessments

Study Period	Prescreen	Screening[4]	Baseline	Treatment																EOT[22]	Post treatment Follow Up	
Month	--	--	--	1									2	3	4	5	6	9	12	--	Q6M x8[23]	Q12M x10[24]
Day	--	-42 to -8	-7 to -1	0	1	2	4	7	11	14	21	28	56	84	112	140	168	252	336	--	--	--
Visit Window (days)	--	--	--	--	--	--	--	±2	±2	±2	±3	±3	±7	±7	±7	±7	±7	±7	±7	--	±14	±14
Informed consent (Prescreen)	X																					
HLA typing[1]	X																					
PRAME expression[2]	X																					
Infectious disease monitoring[3]	X																					
Informed consent (Screening/Treatment)[4]		X																				
Inclusion/exclusion criteria		X																				
Demography[5]		X																				
Medical history[5]		X																				
Prior medications (includes anticancer therapy)[5]		X																				
Physical exam (complete)[6]		X																		X		
Weight		X	X																			
Apheresis[7]		X																				
Lymphodepletion[8]			X																			
STUDY TREATMENT																						
BPX-701 T cell infusion[10]				X																		
Rimiducid infusion[12]					As indicated to treat uncontrolled treatment-emergent toxicity; see Appendix 3																	
SAFETY ASSESSMENTS																						
ECOG performance status		X	X[9]	X[11]				X		X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[13]			X[9]	X[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam (symptom-directed)[6]			X	X[11]				X		X	X	X	X	X	X	X	X	X	X		X	
Neurological exam, MMSE[14]				X[14]	X	X	X	X		X	X	X	X									
ECHO/MUGA[15]		X																				
Adverse events[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
LABORATORY ASSESSMENTS																						
Hematology		X	X[9]	X[11]				X		X	X	X	X	X	X	X	X	X	X	X		
Chemistry		X	X[9]	X[11]				X		X	X	X	X	X	X	X	X	X	X	X		

Study Period	Prescreen	Screening[4]	Baseline	Treatment																EOT[22]	Post treatment Follow Up	
Month	--	--	--	1									2	3	4	5	6	9	12	--	Q6M x8[23]	Q12M x10[24]
Day	--	-42 to -8	-7 to -1	0	1	2	4	7	11	14	21	28	56	84	112	140	168	252	336	--	--	--
Visit Window (days)	--	--	--	--	--	--	--	±2	±2	±2	±3	±3	±7	±7	±7	±7	±7	±7	±7	--	±14	±14
Coagulation		X	X[9]	X[11]				X		X	X	X	X	X	X	X	X	X	X	X		
Urinalysis		X	X[9]																			
Serum pregnancy test		X	X[9]									X	X	X	X	X	X	X	X	X		
Testicular toxicity monitoring[17]			X									X	X	X	X	X	X			X		
Cytokines[18]			X[9]	X[18]	X	X	X	X	X	X	X	X	X							X		
BPX-701 T cell tracking and functional activity[19]			X[9]	X[19]	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
Gene therapy monitoring[20]			X[9]											X			X				X	X
Tumor biopsy (Arm 2 only)[21]			X[9]							X[21]										X[21]		
EFFICACY ASSESSMENTS																						
ARM 1 (AML/MDS)																						
Tumor analysis – peripheral blood[25]		X[26]	X[9,27]	X[11]								X	X	X	X	X	X	X	X[25]			
Tumor analysis – bone marrow		X[26]	X[9,27]									X[28]		X[28]			X[28]		X[28]			
ARM 2 (Uveal melanoma)																						
Radiographic tumor imaging and response assessment		X[29]	X[9,30]									X[31]		X[31]								
ARM 1 & ARM 2 (All subjects)																						
Vital status																					X	
Subsequent anticancer therapy																				X	X	

1. If not part of prior medical records at the time of consent for Prescreening.
2. Centralized testing for PRAME expression in a fresh bone marrow aspirate (AML/MDS) or FFPE tumor tissue biopsy (uveal melanoma). Refer to Section 8.4.1.
3. Blood sample for infectious disease evaluation must be collected within 7 days of planned apheresis. Refer to Section 8.2.8 for panel scope.
4. Only for HLA-A2.01+ subjects with documented positive PRAME expression and no evidence of active infectious disease per Prescreening evaluation.
5. As described in Section 8.1.
6. As described in Section 8.2.3. Obtain standing height at Screening only.
7. Perform as described in Section 7.2 between Day -40 and Day -21 or as approved by the sponsor. Subjects (Arms 1 and 2) must have adequate bone marrow function and subjects (Arm 1 only) must be ≥14 days since the last dose of ongoing or prior anticancer therapy at the time of apheresis.
8. Cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 IV on Day -5, Day -4, and Day -3 prior to the planned BPX-701 infusion on Day 0. Refer to Section 7.3.
9. Must be performed prior to initiation of lymphodepletion.
10. Administer by IV infusion over 15-30 minutes as described in Section 7.4 and the Pharmacy Manual. Subjects should be monitored for safety ≥4 hours after the end of the infusion and released once clinically stable.

11. Must be performed prior to BPX-701 infusion.
12. *FOR QUALIFYING SUBJECTS ONLY (as defined in Section 7.6):* Administer by IV infusion over 2 hours as described in Section 7.5 and the Pharmacy Manual. Subjects should be monitored for safety ≥4 hours after the end of the infusion and released once clinically stable. All required post-infusion time points for blood sample collection, electrocardiogram assessments, and clinic visits will be performed relative to rimiducid administration. Refer to Appendix 3 for additional details.
13. As described in Section 8.2.2. On infusion days (Day 0 for BPX-701 and each dose of rimiducid, if applicable), collect prior to infusion (-60 to -5 min) and at 15 min, 30 min, 1 hr, 2 hr, and 4 hr (± 5 min) after the start of the infusion, and thereafter as clinically indicated until completion of the post-infusion safety monitoring period.
14. As described in Section 8.2.4. On Day 0, perform prior to the BPX-701 infusion (-60 to -5 min) and 4hr (± 30 min) after the start of the infusion. Additional assessments may be performed on infusion days or at any time thereafter as clinically indicated; all neurological exams should be accompanied by an MMSE.
15. LVEF determination by ECHO or MUGA as described in Section 8.2.5. Historical results may be obtained from medical records if performed within 6 weeks of Screening.
16. Collect from date of informed consent (Prescreen) according to safety reporting periods defined in Section 9.6. Refer to Section 9.2 for the definition of an AE.
17. As described in Section 8.2.8. Additional time points should be collected as clinically indicated.
18. Refer to Section 8.2.8 and Section 8.4.3 for panel scope. On Day 0, collect blood samples (serum) prior to the BPX-701 infusion and at 1, 4, and 24 hr after the start of the infusion; for each time point, duplicate samples should be collected for local and central assessment, respectively. Refer to Appendix 2 and Appendix 3 for additional details.
19. Refer to Section 8.2.8 and Section 8.4.2 for panel scope. On Day 0, collect whole blood samples prior to the BPX-701 infusion and at 1, 4, and 24 hr after the start of the infusion; for each time point, duplicate samples should be collected for local and central assessment, respectively. Refer to Appendix 2 and Appendix 3 for additional details.
20. As described in Section 8.4.6.
21. As described in Section 8.4.5. Required pretreatment and on-treatment tumor biopsy for subjects with uveal melanoma. Collect pretreatment sample at Baseline prior to lymphodepletion. Collect on-treatment sample between Days 14 and 21. An additional biopsy at disease progression (EOT visit) is requested, if feasible. Refer to the Laboratory Manual for sample collection procedures.
22. Twelve months after the BPX-701 infusion, or at the time disease progression is confirmed or the subject is discontinued unless the subject has died, is lost to follow-up, or has withdrawn consent for study participation. Visit should be completed before starting any subsequent anticancer treatment. If a subject is unable to return for EOT, the subject should be contacted to collect information on any unresolved AEs. Serum pregnancy test (female subjects) or testicular toxicity monitoring (male subjects) is required if not performed within the past 28 days.
23. Months 18, 24, 30, 36, 42, 48, 54, and 60 from the BPX-601 T cell infusion. Refer to Section 8.4.6.
24. Years 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 from the BPX-701 T cell infusion. Refer to Section 8.4.6.
25. Complete blood count including white blood cell differential and myeloid blast percentage. Samples may be collected more frequently if clinically indicated. Following Month 12, peripheral blood sample are required every 4 weeks (±7 days) for 12 months then every 12 weeks (±7 days) until disease progression or relapse, the start of new anticancer therapy, withdrawal, or study end. If a subject discontinues the study for reasons other than progression or relapse, continue peripheral blood assessments per standard of care frequency until documented progression/relapse, withdrawal, or study end. Response assessment by the investigator using ELN criteria for AML (Appendix 9) or IWG criteria for MDS (Appendix 10).
26. Screening peripheral blood sample as well as aspirate or biopsy to assess bone marrow morphology including myeloid blast count, genetics and mutation profiling, and immunophenotyping. Standard of care assessments if performed within 6 weeks of Screening may be used to characterize disease status. Refer to Section 8.1.2.

27. Baseline peripheral blood sample as well as aspirate or biopsy within 14 days of BPX-701 infusion and following the last dose of any salvage chemotherapy administered after apheresis. Imaging required to document known or suspected CNS involvement; if positive, perform lumbar puncture. Perform additional imaging techniques as appropriate to document other known or suspected sites of extramedullary disease.
28. Serial aspirate or biopsy samples at the indicated time points after BPX-701 infusion. Samples may be collected more frequently if clinically indicated. Assess of bone marrow morphology including myeloid blast count relative to Baseline. Perform additional marrow analyses (genetics, immunophenotyping) as well as CNS and/or extramedullary disease imaging, as appropriate, to confirm complete or partial remission. Following Month 12, marrow sample are required every 24 weeks (±7 days) until disease progression or relapse, the start of new anticancer therapy, withdrawal, or study end. If a subject discontinues the study for reasons other than progression or relapse, continue marrow assessments per standard of care frequency until documented progression/relapse, withdrawal, or study end. Response assessment by the investigator using ELN criteria for AML (Appendix 9) or IWG criteria for MDS (Appendix 10).
29. Radiologic evidence of measurable disease required at Screening to confirm subject eligibility. Standard of care assessments if performed within 6 weeks of Screening may be used to assess disease status.
30. CT scan with contrast of the chest, abdomen, and pelvis plus MRI to document known or suspected liver and CNS metastases (all subjects) within 28 days of BPX-701 infusion. Bone scan required to document known or suspected bone metastases, if applicable. Refer to Section 8.6.
31. Use the same assessment technique for tumor imaging throughout the study. Radiographic assessments required at Day 28, followed by every 8 weeks (±7 days) for the first year following BPX-701 T cell infusion, then every 12 weeks (±7 days) for the second year, then annually until confirmed disease progression, the start of new anti-cancer therapy, withdrawal, or study end. If a subject discontinues the study for reasons other than progressive disease, continue imaging per standard of care frequency until documented disease progression, withdrawal, or study end. Response assessment by the investigator using RECIST v1.1 (Appendix 7). Confirmation of response or disease progression is required as described in Section 8.6.

13.2 Appendix 2: Biomarker Sampling Schedule during Treatment Month 1 (Day 0 thru Day 28)

Study Period:	**Treatment**										
Month:	**1**										
Day:	**0**			**1**	**2**	**4**	**7**	**11**	**14**	**21**	**28**
Scheduled collection time	**Pre-infusion[1]**	**Post-infusion start[2]**			**During visit**						
		1hr	**4hr**	**24hr**							
Sample collection window (min)	**-60 to -5**	**±5**	**±5**	**±60**	**--**	**--**	**--**	**--**	**--**	**--**	**--**
Blood sample (serum) for cytokines[3, 4]	X	X	X	X	X	X	X	X	X	X	X
Whole blood sample for BPX-701 T cell tracking and functional activity[3, 4]	X	X	X	X	X	X	X	X	X	X	X

1. BPX-701 T cell infusion.
2. Scheduled time points are relative to the start of the infusion.
3. Refer to Laboratory Manual for detailed sample collection, processing, and shipment instructions.
4. Samples may be collected more frequently as clinically indicated. For subjects with signs or symptoms of CRS or neurotoxicity (Section 7.6.2), collect at the time of event as described in Section 7.6.4.

13.3 Appendix 3: Pharmacokinetics, ECG, and Safety Biomarker Sampling Schedule for Subjects that receive Rimiducid

Study Period:	**Treatment**						
Scheduled collection time	**Pre-infusion[1]**	**Post-infusion start[2]**					**Every 24hr thereafter until symptom resolution**
		1hr	**2hr**	**4hr**	**8hr**	**24hr**	
Sample collection window (min)	**-60 to -5**	**±5**	**-5[4]**	**±5**	**±5**	**±60**	**±60**
Blood sample (plasma) for rimiducid PK[6]	X[3]	X[3]	X[3]	X[3]	X[3]	X	
Electrocardiogram[5]	X	X	X	X	X	X	
Blood sample (serum) for cytokines[6,7]	X	X	X	X		X	X
Whole blood sample for BPX-701 T cell tracking and functional activity[6,7]	X	X	X	X		X	X

1. Rimiducid infusion *FOR QUALIFYING SUBJECTS ONLY (as defined in Section 7.6)*. Administer by IV infusion over 2 hours as described in Section 7.5 and the Pharmacy Manual. Subjects should be monitored for safety ≥4 hours after the end of the infusion and released once clinically stable.
2. Scheduled time points are relative to the start of the FIRST rimiducid infusion ONLY.
3. For all planned PK time points up to 8 hours post-infusion, blood must be collected from a peripheral vein contralateral to the arm/location into which rimiducid is administered.
4. Collect sample just prior to the end of the rimiducid infusion.
5. Prior to each blood sample collection, obtain a time-matched ECG; triplicate assessments no more than 5 mins apart are required if the initial tracing is abnormal, clinically significant.
6. Refer to Laboratory Manual for detailed sample collection, processing, and shipment instructions.
7. Samples may be collected more frequently as clinically indicated. For subjects with signs or symptoms of CRS or neurotoxicity (Section 7.6.2), collect at the time of event as described in Section 7.6.4.

13.4 Appendix 4: Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Adapted from Oken 1982

13.5 Appendix 5: New York Heart Association Criteria

The following table presents the New York Heart Association Classification of Functional Capacity and Objective Assessment:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Classification of Functional Capacity and Objective Assessment. Available at http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp. Accessed 18 June 2018

13.6 Appendix 6: Common Corticosteroids and Conversion Half-Lives

Glucocorticoid	Approximate equivalent dose (mg)	Half-life (hr)	Clearance/ 7 half- lives (DAYS)
Short-Acting			
Cortisone	25	8--12	3.5
Hydrocortisone	20	8--12	3.5
Intermediate-Acting			
Methylprednisolone	4	18--36	10.5
Prednisolone	5	18--36	10.5
Prednisone	5	18--36	10.5
Triamcinolone	4	18--36	10.5
Long-Acting			
Betamethasone	0.6 – 0.75	36--54	15.75
Dexamethasone	0.75	36--54	15.75

Hunter J. (1992). "Second line agents in the treatment of rheumatic diseases." Ann Rheum Dis **51**: 1192.

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13.7 Appendix 7: Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Quick Reference

Eligibility

Only patients with measurable disease at baseline should be included in this protocol.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions:

- **Tumor lesions** must be accurately measured in at least one dimension with longest diameter ≥10mm by CT scan (slice thickness ≤5 mm), ≥10mm caliper measurement by clinical exam, ≥20mm by chest x-ray.
- **Malignant lymph nodes** must be considered pathologically enlarged and measurable with a diameter ≥15mm in the short axis when assessed by CT scan (slice thickness ≤5 mm)

Non-measurable lesions - all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions, i.e., leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are neither confirmed nor followed by reproducible imaging techniques.

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging is preferred.

Methods of Measurement

CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT should be performed with cuts of 5mm or less in slice thickness contiguously. MRI is also acceptable in certain situations (e.g., for body scans).

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, chest CT is preferable.

Ultrasound is not a useful assessment of lesion size and should not be used as a method of measurement as they are not reproducible and operator dependent. If new lesions are identified by ultrasound, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for ***all target lesions*** will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but these lesions should be followed as 'present', 'absent', or 'unequivocal progression'.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5mm. The appearance of 1 or more new lesions is also considered progression
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters since treatment started

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until the end of treatment considering any requirement for confirmation. In general, the patient's best response assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Unevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of confirmed PR or confirmed CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Adapted from Eisenhauer 2009

13.8 Appendix 8: Immune-Related Response Criteria (irRC)

Under immune-related Response Criteria (irRC), antitumor response is based on the total measurable tumor burden. For irRC, only index and measurable new lesions are considered. To calculate baseline tumor burden, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions is obtained. All index lesions include up to 5 lesions per organ, up to 10 visceral lesions and 5 cutaneous index lesions. At each subsequent tumor assessment, the SPD of index lesions and of new, measurable lesions (≥5 x 5mm; up to 5 new lesions per organ: 5 new cutaneous lesions, and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Time-point response assessment using irRC involves percentage changes in tumor burden per assessment time point which describes the size and growth kinetics of both conventional and new, measurable lesions upon their appearance. At each tumor assessment, the response in index and new, measurable lesions is defined and based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed in relation to baseline measurements (i.e. the SPD of all index lesions at screening).

Overall response assessment (according to irRC) is derived from the time-point assessments, which is based on tumor burden, and as listed below:

Measurable Response	**Non-Measurable Response**		**Overall Response**
Index and new, measurable lesions (tumor burden), *%	Non-index lesions	New, non-measurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

* Decreases assessed are relative to baseline, including measurable lesions only (>5 x 5 mm).

† Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Response/Lesion Categories	irRC Response definition
New, measurable lesions (i.e. ≥5 x 5 mm)	Incorporated into tumor burden
New, measurable lesions (i.e. <5 x 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining irCR (complete disappearance required)
irCR	Complete disappearance of all lesions (whether measurable, or not), and no new lesions, in two consecutive observations not less than 4 weeks apart
irPR	≥50% decrease in tumor burden, compared with baseline, in two consecutive observations at least 4weeks apart
irSD	Not meeting criteria for irCR or irPR, in the absence of irPD
irPD	At least 25% increase in tumor burden relative to nadir (minimum recorded tumor burden), confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Adapted from Wolchok 2009

13.9 Appendix 9: ELN Response Criteria for AML

CATEGORY	DEFINITION
RESPONSE	
CR without MRD (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-PCR, or CR with negativity by MFC
CR	• Bone marrow blasts <5% • Absence of circulating blasts and blasts with Auer rods • Absence of extramedullary disease • ANC ≥1.0 x 10^9/L • Platelets ≥100 x 10^9/L • MRD^+ or unknown
CR with incomplete hematologic recovery (CR_i)	All CR criteria except: o Residual neutropenia (<1.0 x 10^9/L); or, o Thrombocytopenia (<100 x 10^9/L)
Morphologic leukemia-free state (MLFS)	• Bone marrow blasts <5% • Absence of circulating blasts and blasts with Auer rods • Absence of extramedullary disease • No hematologic recovery required • Marrow should not merely be aplastic; at least 200 cells should be enumerated, or cellularity should be ≥10%
PR	• All hematologic criteria of CR • Decrease of bone marrow blast percentage to 5% to 25% • Decrease of pretreatment bone marrow blast percentage by ≥50%
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for progressive disease not met for ≥3 months
Progressive disease	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in blood: o >50% increase in marrow blasts over baseline (a minimum 15%-point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage >70% over ≥3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 x 10^9/L, and/or platelet count to >50 x 10^9/L nontransfused); or o >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (in the absence of differentiation syndrome[1]); or, o New extramedullary disease
RELAPSE	
Hematologic relapse (after CR_{MRD-}, CR, CR_i)	• Bone marrow blasts ≥5%; or, • Reappearance of blasts in the blood; or, • Development of extramedullary disease
Molecular relapse (after CR_{MRD-})	If studied pretreatment, recurrence of MRD as assessed by RT-PCR or MFC
TREATMENT FAILURE	
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Death occurring before completion of therapy, or <7 days following its completion; or death occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available

ANC=absolute neutrophil count; CR=complete remission; MFC=multiparameter flow cytometry; MRD=minimal residual disease; PR=partial remission; RT-PCR=reverse transcription polymerase chain reaction

1. Transient increase in percentage of bone marrow blasts and an absolute increase in blood blasts

Adapted from Dohner 2017

13.10 Appendix 10: IWG Response and Hematological Improvement Criteria for Myelodysplasia

CRITERIA FOR RESPONSE	
Category	**Description (responses must be last ≥4 weeks)**
Complete remission	Bone Marrow: ≤5% blasts with normal maturation of cell lines[1] Peripheral Blood: • Hgb ≥11 g/dL • Platelets ≥100 x 10^9/L • Neutrophils ≥1.0 x 10^9/L • Blasts 0%
Partial remission	Same as complete response except bone marrow blasts decreased by ≥50% over pretreatment but still >5% Cellularity and morphology not relevant
Marrow CR	Bone Marrow: ≤5% blasts and decrease ≥50% over pretreatment Peripheral Blood: if HI responses, note in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in bone marrow blast %, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast % • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete: disappearance of the chromosomal abnormality without the appearance of new ones Partial: ≥50% reduction of the chromosomal abnormality
Disease progression	For subjects with: • <5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to >10% blasts • 10-20% blasts: ≥50% increase to >20% blasts • 20-30% blasts: ≥50% increase to >30% blasts Any of the following: • ≥50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥2 g/dL • Transfusion dependence
CRITERIA FOR HEMATOLOGICAL RESPONSE	
Hematologic improvement[2]	**Description (responses must be last ≥8 weeks)**
Erythroid response (pretreatment <11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of ≥4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet response (pretreatment <100 x 10^9/L)	Absolute increase ≥30 x 10^9/L for patients starting with >20 x 10^9/L platelets Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100%
Neutrophil response (pretreatment <1.0 x 10^9/L)	≥100% increase and an absolute increase >0.5 x 10^9/L
Progression or relapse after HI[3]	At least one of the following: • ≥50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥1.5 g/dL

	• Transfusion dependence

CR=complete remission; FAB=French American British; Hgb=hemoglobin; HI=hematological improvement; PR=partial response; RBC=red blood cell

1. Persistent dysplasia will be noted; dysplastic changes should consider the normal range of dysplastic changes.
2. Pretreatment counts average of at least 2 measurements (not influenced by transfusions) ≥1 weeks apart.
3. In the absence of another explanation, such as acute infection, repeated courses of chemotherapy, gastrointestinal bleeding, hemolysis, and so forth. It is recommended that 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Adapted from Cheson 2006