THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Phase 1/2 Trial Evaluating Treatment of Emergent Graft versus Host Disease (GvHD) With AP1903 After Planned Donor Infusions (DLIs) of T- cells Genetically Modified with the iCasp9 Suicide Gene in patients with Hematologic Malignancies 2012-0501

Core Protocol Information

Short Title	DLI of T-cells genetically modified with iCasp9 Suicide Gene
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Full Title:	A Phase 1/2 Trial Evaluating Treatment of Emergent Graft versus Host Disease (GvHD) With AP1903 After Planned Donor Infusions (DLIs) of T- cells Genetically Modified with the iCasp9 Suicide Gene in patients with Hematologic Malignancies
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objective:
To evaluate the safety of the infusion of inducible caspase 9 (BPZ-1001) modified T-cells followed by dimerizer drug, AP1903.

1.2 Secondary Objectives:
1.2.1 To assess at 6 months post donor lymphocyte infusion (DLI):
- a. Disease-free survival,
- b. Non-relapse mortality,
- c. Chimerism,
- d. Overall incidence of acute and chronic graft-versus-host disease (GvHD),
- e. Overall incidence of systemic infections.
- f. Time to resolution of GvHD.

1.2.2 To assess the incidence of Epstein-Barr virus (EBV)-associated lymphoproliferative disorder or EBV reactivation requiring therapy post DLI.
1.2.3 To assess the proportion of patients developing grade I-IV acute GvHD by Day 28, 56, and 180 post DLI.
1.2.4 To assess the proportions of GvHD complete response (CR), partial response (PR), mixed response, no response, and progression among surviving patients at Day 3, 7, 14, 28, and 56 post-administration of AP1903.
1.2.5 To assess the incidence of GvHD treatment failure, defined as: no response, progression, administration of additional therapy for GvHD, or mortality, at Day 3, 7, 14, 28, and 56 post-administration of AP1903.
1.2.6 To assess the incidence of acute GvHD flare after CR/PR requiring additional agent (including 2.5
mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) for systemic therapy before Day 56 post-administration of AP1903.
1.2.7 To determine the change in patient-reported outcomes from enrollment to Day 56 post-administration of AP1903.

2.0 Background and Rationale

2.1 Allogeneic stem cell transplantation
Allogeneic stem cell transplantation is an effective treatment for a broad range of hematologic malignancies, mediated in large part by a potent graft-vs-malignancy effect mediated by donor T-cells.[7-9] Graft-vs.-host disease is also mediated by alloreactive T-cells, reacting against major and minor histocompatibility antigens of the recipient.[10,11] Some of these alloantigens are expressed by malignant cells and are targets for graft-vs-leukemia (GVL) effects.[12,13] It is a major challenge to separate GVL from GvHD.

2.2 Acute Graft vs Host Disease
Acute graft-versus-host disease (GvHD) is the major complication of allogeneic hematopoietic stem cell (HSC) transplantation.[14] Acute GvHD produces significant morbidity and complicates patient management, resulting in organ toxicity, frequent infections, malnutrition and substantial delay in recovery from transplantation.

Acute GvHD usually occurs within the first 3-4 months of allogeneic HSCT and may involve the skin, liver and intestinal tract. It is believed that T-lymphocytes contained in the donor graft respond in vivo to disparate major (HLA) or minor (non-HLA) histocompatibility antigens expressed by recipient tissues, initiating a cascade of events leading to the signs and symptoms of acute GvHD.[14]

The syndrome of acute GvHD includes signs and symptoms affecting the skin, GI tract, and liver. Skin

involvement (maculopapular exanthem) is usually the first sign. Lesions may be pruritic or painful, red to violaceous in color, and often involve the palms and soles. Acute GvHD of the gut may involve the stomach, small bowel and colon producing persistent nausea and vomiting or profuse diarrhea, intestinal bleeding, cramping abdominal pain and ileus. Liver GvHD produces cholestatic liver injury with hyperbilirubinemia and, in some cases, hepatocellular enzyme elevations.

GVHD occurring following allogeneic stem cell transplantation has a complex pathophysiology. The chemotherapy preparative regimen produces toxicity and upregulates inflammatory cytokines, which then augment the graft-vs-host immune reaction. The threshold T-cell dose to induce GVHD in an HLA identical allograft is approximately 10^5 T-cells/kg at the time of allogeneic stem cell transplantation. A given dose of T-cells is less likely to produce GVHD if given late after the acute inflammation and toxicity after the preparative regimen and the transplant have resolved. This threshold is approximately $3x10^6$ to 10^7 T-cells/kg when given as a delayed donor lymphocyte infusion.[9]

2.3 T-Cell Depletion with Alemtuzumab to Reduce GvHD

Depletion of T-cells from the transplant is an effective method of preventing GvHD, but increases the risk of graft rejection and leukemia/lymphoma relapse due to the loss of the T-cell mediated GVL effect.[32-36] In vivo depletion of T-cells at the time of HSCT with a systemic T-cell depleting antibody, alemtuzumab, is also effective in preventing GvHD [37,38] and reducing non-relapse mortality, but the risk of relapse of malignancy is increased,[39-42] and overall survival has not been improved. In vivo alemtuzumab also delays immune reconstitution, leading to frequent infections and potential loss of graft-versus-tumor responses. In a study evaluating dose de-escalation of alemtuzumab from 60mg to 20mg in 4 sequential cohorts, in the context of fludarabine-melphalan conditioning and human leukocyte antigen (HLA)-identical sibling transplantation, the 20mg dose was also associated with greater risk of severe GvHD (acute grade III-IV or chronic extensive) compared with > 20mg (hazard ratio, 6.7; 95% CI, 2.5-18.3). In contrast, dose reduction to 30 mg on day -1 was associated with equivalent clinical outcomes to higher doses but better lymphocyte recovery at 12 months.[43] Only 4% of patients receiving 30 mg of CAMPATH developed any Gr II-IV aGvHD and only 7% developed Gr III-IV aGVH or extensive cGvHD.

2.4 Donor Lymphocyte Infusion

Subsequent infusion of donor T-cells by donor lymphocyte infusion (DLI) has become a standard of care for some transplant patients [44] because it can induce remission in some patients with recurrent myeloid and lymphoid malignancies,[45-48] but GvHD remains a major complication. The incidence of GvHD is reduced when administration of allogeneic T-cells is delayed for many months after the transplant. Graded doses may be tolerated and induce remission of malignancy, but GvHD remains the major complication. [49,50] As DLI doses required to restore full immunocompetence are reached, the frequency and severity of GvHD rises in tandem. Hence, if one could minimize the risk of uncontrolled GvHD for the minority, the ability to give an effective DLI does in the majority would increase significantly.

One standard approach is the use of a T-cell depleted transplant or a transplant with systemic T-cell depleting antibody, alemtuzumab, as a means to achieve engraftment without GvHD, followed later by donor lymphocyte infusion (DLI) given as a planned T cell infusion strategy prior to relapse to restore immunocompetency, improve engraftment, and increase GVL effects.[51-53] This is a promising approach to prevent or treat relapse, but if the DLI is given within 3 months, a high rate of GvHD has resulted. One strategy would be to utilize genetically modified T-cells, transducing them to express a suicide gene to allow eradication of transplanted T-cells, including alloreactive T-cells causing GvHD, when GvHD occurs, abrogating the process of GvHD. While a theoretically attractive approach to this problem, the practical development of such a suicide gene switch system has until recently remained elusive.

2.5 Inducible caspase 9 (iCasp9) suicide gene

iCasp9-mediated suicide is based on conditional dimerization of a chimeric version of the pro-apoptotic molecule, caspase 9, that is constructed from human proteins and therefore less likely to be immunogenic.54 iCasp9 is generated by joining a drug-binding domain to human caspase 9. The

drug-binding domain consists of human FK506-binding protein (FKBP12) with an F36V mutation. This point mutation increases the binding affinity of FKBP12 to non-toxic synthetic homodimerizers, AP1903.55 Administration of AP1903 dimerizes and activates caspase 9; this activates downstream caspases, obligating cellular apoptosis within 24 hours.

iCasp9 has numerous advantages over other suicide genes, like the herpes simplex virus thymidine kinase (HSVtk), which has been evaluated in Phase II trials with limited success.56 iCasp9 carries significant advantages over HSVtk, including its composition from human derived proteins, making it less likely to be immunogenic, its ability to kill cells in a cell cycle-independent fashion and thus not restricted to dividing cells, and finally the use of a non-toxic, targeted activation agent, AP1903, that does not preclude the use of ganciclovir as prophylaxis or treatment of cytomegalovirus disease.

2.6 Preliminary data indicate the feasibility of this approach

Di Stasi, Brenner et al.[57] conducted a phase I study evaluating the feasibility of this approach. These investigators infused iCasp9-expressing T lymphocytes, in an effort to enhance immune recovery and reduce infection/relapse following transplantation of HLA-haploidentical hemopoietic (CD34+) stem cells as treatment for high-risk, relapsed leukemia. The infused T-cells were first depleted of alloreactive progenitor cells after stimulation with recipient irradiated, EBV-transformed lymphoblastoid cells (40:1) for 72 hrs, and subsequent exposure to a CD25-directed immunotoxin (RFT5-dgA). The allodepleted cells were then transduced with a retroviral vector encoding the iCasp9 suicide gene and a selection marker (Δ CD19), which allowed enrichment to >95% purity.

Three patients received $1x10^6$ (one of three treated off protocol), two patients received $3x10^6$ and two patients received 1×10^7 gene-modified T-cells/kg. Forced expression of a transgenic caspase-derived molecule did not preclude *in vivo* survival or expansion of infused T-cells, which became detectable by flow cytometry (CD3+ΔCD19+cells) and by Q-PCR (for iCasp9) within 7 days of infusion. The iCasp9+ T-cells contained both CD4+ and CD8+ subsets, were viral-reactive (CMV, EBV, and ADV) and polyclonal, and have now persisted beyond 620 days. Four of the 6 enrolled patients subsequently developed grade I/II acute GvHD of skin, with one also developing liver GvHD. As per protocol, these patients received a single dose of dimerizer agent. Within 30 minutes of completing AP1903 administration, a >90% reduction of transgenic T-cells was observed, as assessed by flow cytometry for CD3+CD19+ T-cells and by Q-PCR amplification for iCasp9. This effect was followed within 36 hrs by resolution of all aGvHD, showing that the iCasp9 transgene can be functional *in vivo* and can rapidly deplete sufficient T-cells to control GvHD. Of note, the residual allodepleted T-cells were no longer associated with GvHD but were still able to re-expand within 1 to 2 weeks and contained subpopulations that preserved reactivity to viruses (CMV) and fungi (Aspergillus fumigatus), as assessed by IFN-ã production. Of these seven patients, two died from progressive disease without GvHD or steroid use at the time of death (day 585 post HSCT and day 155 post HSCT), one of whom who had persistent active ALL at the time of transplant. None have died of transplant related complications. None of the remaining patients have active GvHD or require steroids for the treatment of GvHD and none have developed chronic GvHD. Three additional patients have been enrolled at the 1×10^7 gene-modified T-cells/kg dose and are awaiting infusion of cells.

In conclusion, administration of small numbers of iCasp9+ allodepleted T-cells has produced CD4+ and CD8+ T-cell reconstitution after haplo-identical, CD34+ SCT, while administration of the small molecule dimerizer agent AP1903 has rapidly ablated residual allo-reactive T-cells and abrogated early GvHD, whilst preserving anti-viral specificity, with long term GvDH-free survival without the requirement for steroids observed.

3.0 Drug Information

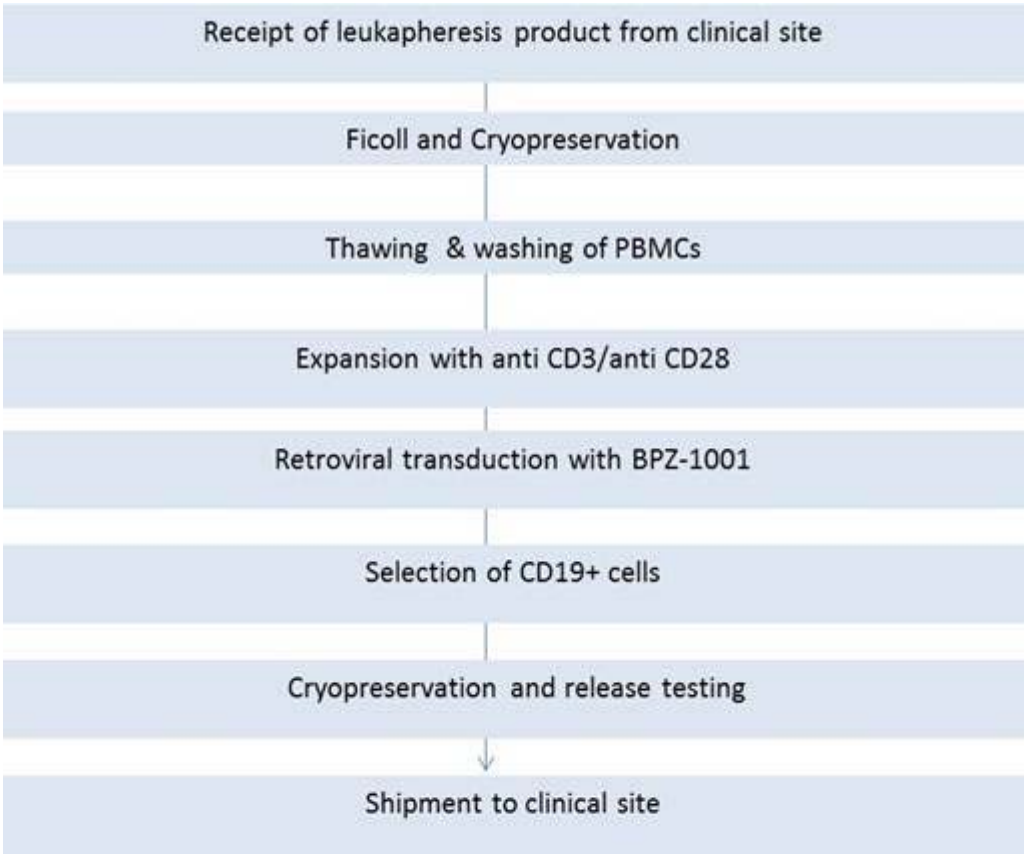
3.0 Investigational Product:

3.1 Donor Lymphocyte Infusion

3.1.1 Generation of Cell Therapy Product

The cell therapy product described in this protocol is iCasp9 (BPZ-1001)-Modified DLI.

Processing Schema



3.1.2. BPZ 1001 Modified DLI Manufacturing process

The starting material for the iCasp-modified DLI production is the donor apheresis. The apheresis product (at 2-8°C) is delivered to Bellicum's centralized GMP manufacturing facility at Lonza Houston Inc (Houston, Texas). After verification of the acceptability of the starting material, the apheresis is placed on the SEPAX device for mononuclear separation, and subsequent cryopreservation in multiple aliquots. At the initiation of manufacturing, an aliquot is transferred to the manufacturing cleanroom and rapidly thawed. The cells are washed and treated with CD3+/CD28+ antibodies, and placed into culture media so that the T-cells will proliferate until achieving a target cell number for transduction. The expanded T cells are transduced with BPZ-1001 retroviral construct containing the iCasp gene and CD19 marker. Post-transduction, the cells are selected for CD19+ surface marker and the enriched T cell population is allowed to proliferate further in order to reach the target dose of CD3+/CD19+ cells. The cells are formulated with the cryopreservation media (CryoStor CS10) and cryopreserved. The final iCasp-modified DLI product is stored cryopreserved in the LN2 vapor phase until release testing is complete. The final iCasp-modified DLI product will be delivered to MDACC in the LN2 vapor phase in validated cryoshippers.

3.1.3. Product Packaging, Labeling, Storage and Shipping

3.1.3.1. ICASP MODIFIED DLI Product Packaging, Labeling and Storage

Packaging and Formulation
ICasp modified DLI T cells are cryopreserved in 10-15mL freezing medium (Cryostor CS10, BioLife) and are stored frozen in cryostorage bags in the vapor phase of liquid nitrogen.

Labeling
The product label (directly applied to the primary container) includes the Subject specific lot number, cryopreservation date, T cell dose, storage conditions, sponsor, and product name. All products manufactured under the IND are also labeled with: "Caution: New Drug-Limited by Federal Law to Investigational Use" per 21 CFR 312.6.

Shipping and Storage
Cryopreserved ICasp modified DLI will be delivered in liquid nitrogen vapor phase to the clinical site (MDACC) in a validated shipping container. The receiving cell processing laboratory will store the product in vapor phase of LN2 until time of infusion. At that time, the product will be rapidly thawed at 37° C ± 2°C per standard operating procedures for infusion to the recipient.

3.1.3.2. AP1903 Dimerizer drug Packaging, Labeling and Storage

Packaging and Formulation
The AP1903 for Injection is packaged in 10 mL Type 1 clear glass serum vials. The contents of each vial is composed of the labeled content (40 mg) of AP1903 drug substance dissolved in a sterile, endotoxin free, 24% Solutol HS 15/Water for Injection solution at an AP1903 concentration of 5 mg/mL and at pH 5.0 – 7.5. Each vial is stoppered with a Teflon© coated serum stopper and a yellow flip-off seal.

Labeling
The primary product label (applied directly to the vial) for the AP1903 for Injection will contain the following information: product name, AP1903 for Injection; the manufacturers' lot number; product concentration, 5 mg/mL; volume of solution available in the vial; total AP1903 contents of the vial (40 mg); a statement, "For IV Administration, contains no preservatives" and the IND notation, "Caution: New Drug-Limited by Federal Law to Investigational Use".

Storage
The AP1903 for Injection vials must be stored at 5°C ± 3°C (41°F ± 5°F) in a limited access, qualified refrigerator, preferably without light.

Preparation for Treatment
For use, the AP1903 will be diluted prior to administration. The AP1903 is administered via i.v. infusion at a dose of 40mg diluted in 100ml physiological saline and administered over 2 hours using a DEHP-free saline bag and solution set which will be provided by Bellicum Pharmaceuticals.

3.1.4. Supply and Return of Drug
AP1903 will be provided free of charge by Bellicum Pharmaceuticals. Upon completion or termination of the study, all unused and/or partially used AP1903 will be destroyed following Investigational Pharmacy policy.

3.1.5. Drug Accountability
The investigator, or designee, must maintain an inventory record of AP1903 received, dispensed, administered and destroyed to assure the Food and Drug (FDA) that the investigational new drug will not be dispensed to any person who is not a patient under the terms and conditions set forth in this protocol.

3.2. Preparative Regimen for Transplant

3.2.1. Melphalan

Therapeutic Classification.

Alkylating agent.

Stability and storage.

Store Melphalan at room temperature, between 59 and 86 degrees F (15 and 30 degrees C). Store away from heat, moisture, and light.
Melphalan should be handled at temperatures greater than 5 degrees C for a minimum of time, but solutions of the drug can be stored for at least 6 and possibly up to 12 months at -20 degrees C without significant deterioration taking place.

Administration.

Oral: Administer on an empty stomach (1 hour prior to or 2 hours after meals)
Parenteral: Due to limited stability, complete administration of I.V. dose should occur within 60 minutes of reconstitution

I.V.: Infuse over 15-30 minutes. Extravasation may cause local tissue damage; administration by slow injection into a fast running I.V. solution into an injection port or via a central line is recommended; do not administer by direct injection into a peripheral vein. Saline-based hydration preceding (2-4 hours), during, and following (6-12 hours) administration reduces risk of drug precipitation in renal tubules.

Adverse Effects.
Observed in more than 10%: Gastrointestinal: Nausea/vomiting (oral low-dose: <10%; I.V.: 30% to 90%), oral ulceration Hematologic: Myelosuppression, leukopenia (nadir: 14-21 days; recovery: 28-35 days), thrombocytopenia (nadir: 14-21 days; recovery: 28-35 days), anemia
Miscellaneous: Secondary malignancy (<2% to 20%; cumulative dose and duration dependent, includes acute myeloid leukemia, myeloproliferative syndrome, carcinoma)

Observed in 1% to 10%: Miscellaneous: Hypersensitivity (I.V.: 2%; includes bronchospasm, dyspnea, edema, hypotension, pruritus, rash, tachycardia, urticaria)

Observed infrequent, frequency undefined, postmarketing, and/or case reports: Agranulocytosis, allergic reactions, alopecia, amenorrhea, anaphylaxis (rare), bladder irritation, bone marrow failure (irreversible), BUN increased, cardiac arrest, diarrhea, encephalopathy, hemolytic anemia, hemorrhagic cystitis, hemorrhagic necrotic enterocolitis, hepatic veno-occlusive disease (I.V. melphalan), hepatitis, injection site reactions (ulceration, necrosis), interstitial pneumonitis, jaundice, ovarian suppression, pruritus, pulmonary fibrosis, radiation myelopathy, rash (maculopapular), seizure, SIADH, skin hypersensitivity, skin vesiculation, sterility, stomatitis, testicular suppression, tingling sensation, transaminases increased, vasculitis, warmth sensation

Mechanism of action.

Alkylating agent which is a derivative of mechlorethamine that inhibits DNA and RNA synthesis via formation of carbonium ions; cross-links strands of DNA; acts on both resting and rapidly dividing tumor cells.

Human Pharmacology.

Note: Pharmacokinetics listed are for FDA-approved doses.
Absorption: Oral: Variable and incomplete
Distribution: Vd: 0.5-0.6 L/kg throughout total body water; low penetration into CSF
Protein binding: 60% to 90%; primarily to albumin, 20% to á1-acid glycoprotein
Metabolism: Hepatic; chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan

Bioavailability: Unpredictable; 61% ± 26%, decreasing with repeated doses
Half-life elimination: Terminal: I.V: 75 minutes; Oral: 1-2 hours
Time to peak, serum: ~1-2 hours
Excretion: Oral: Feces (20% to 50%); urine (~10% as unchanged drug)

Dose adjustment in renal/hepatic impairment (specific to stem cell transplant).
Renal: I.V.: Autologous stem cell transplant: Serum creatinine >2 mg/dL: Reduce dose from 200 mg/m2 to 140 mg/m2 (Badros, 2001)
Hepatic: Melphalan is hepatically metabolized; however, dosage adjustment does not appear to be necessary.

Monitoring Parameters.
CBC with differential and platelet count, serum electrolytes, uric acid

3.2.2. Fludarabine

Therapeutic Classification.

Antineoplastic agent; Antimetabolite (Purine Analog)

Pharmaceutical Data.

Each vial contains 50 mg lyophilized drug, to be reconstituted with 2 ml sterile water to a solution that is 25 mg/ml for IV administration.

Solution Preparation.

Mix each vial with 2 ml sterile pyrogen-free water to a clear solution, which is 25 mg/ml for IV administration only. Reconstituted solution should be used within 8 hours.

Adverse Effects.
Observed in more than 10%: Cardiovascular: Edema (8% to 19%); Central nervous system: Fever (11% to 69%), fatigue (10% to 38%), pain (5% to 22%), chills (11% to 19%); Dermatologic: Rash (4% to 15%); Gastrointestinal: Nausea/vomiting (1% to 36%), anorexia (34%), diarrhea (5% to 15%), gastrointestinal bleeding (3% to 13%); Genitourinary: Urinary tract infection (2% to 15%); Hematologic: Myelosuppression (nadir: 10-14 days; recovery: 5-7 weeks; dose-limiting toxicity), anemia (14% to 60%), neutropenia (grade 4: 37% to 59%; nadir: ~13 days), thrombocytopenia (17% to 55%; nadir: ~16 days); Neuromuscular & skeletal: Weakness (9% to 65%), myalgia (4% to 16%), paresthesia (4% to 12%); Ocular: Visual disturbance (3% to 15%); Respiratory: Cough (≤44%), pneumonia (3% to 22%), dyspnea (1% to 22%), upper respiratory infection (2% to 16%), rhinitis (≤11%); Miscellaneous: Infection (12% to 44%), diaphoresis (≤14%)

Observed in 1% to 10%: Cardiovascular: Peripheral edema (less than 7%), angina (less than 6%), chest pain (less than 5%), CHF (3%), arrhythmia (3%), cerebrovascular accident (3%), MI (3%), supraventricular tachycardia (3%), deep vein thrombosis (1% to 3%), phlebitis (1% to 3%), aneurysm (less than 1%), transient ischemic attack (1%); Central nervous system: Headache (9%), malaise (6% to 8%), sleep disorder (1% to 3%), cerebellar syndrome (less than 1%), depression (1%), mentation impaired (1%); Dermatologic: Alopecia (3%), pruritus (1% to 3%); Endocrine & metabolic: Hyperglycemia (1% to 6%), LDH increased (less than 6%), dehydration (1%); Gastrointestinal: Abdominal pain (10%), stomatitis (9%), weight loss (6%), esophagitis (3%), constipation (1% to 3%), mucositis (2%), dysphagia (1%); Genitourinary: Dysuria (3% to 4%), hesitancy (3%); Hematologic: Hemorrhage (1%), myelodysplastic syndrome/acute myeloid leukemia (usually associated with prior or concurrent treatment with other anticancer agents); Hepatic: Cholelithiasis (3%), liver function tests abnormal (1% to 3%), liver failure (1%); Neuromuscular & skeletal: Back pain (9%), osteoporosis (2%), arthralgia (1%); Otic: Hearing loss (2% to 6%); Renal: Hematuria (2% to 3%), renal failure (1%), renal function test abnormal (1%),

proteinuria (1%); Respiratory: Bronchitis (9%), pharyngitis (9%), allergic pneumonitis (6%), hemoptysis (1% to 6%), sinusitis (5%), epistaxis (1%), hypoxia (1%); Miscellaneous: Flu-like syndrome (5% to 8%), herpes simplex infection (8%), anaphylaxis (1%), tumor lysis syndrome (1%)

Observed in <1%, postmarketing, and/or case reports: Acute respiratory distress syndrome, agitation, blindness, blurred vision, bone marrow fibrosis, coma, confusion, diplopia, eosinophilia, Epstein-Barr virus (EBV) associated lymphoproliferation, EBV reactivation, erythema multiforme, Evans syndrome, flank pain, hemolytic anemia (autoimmune), hemophilia (acquired), hemorrhagic cystitis, herpes zoster reactivation, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, interstitial pneumonitis, metabolic acidosis, opportunistic infection, optic neuritis, optic neuropathy, pancreatic enzymes abnormal, pancytopenia, pemphigus, pericardial effusion, peripheral neuropathy, photophobia (primarily with high doses), progressive multifocal leukoencephalopathy (PML), pulmonary fibrosis, pulmonary hemorrhage, pulmonary infiltrate, respiratory distress, respiratory failure, Richter's syndrome, seizure, skin cancer (new onset or exacerbation), Stevens-Johnson syndrome, thrombocytopenia (autoimmune), thrombocytopenic purpura (autoimmune), toxic epidermal necrolysis, trilineage bone marrow aplasia, trilineage bone marrow hypoplasia, urate crystalluria, wrist drop

Also observed: Neurologic syndrome characterized by cortical blindness, coma, and paralysis [36% at doses >96 mg/m2 for 5-7 days; <0.2% at doses <125 mg/m2/cycle (onset of neurologic symptoms may be delayed for 3-4 weeks)]
Mechanism of Action.
Fludarabine inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase; also inhibits DNA primase and DNA ligase I.
Human Safety and Pharmacology.

Distribution: Vd: 38-96 L/m2; widely with extensive tissue binding
Protein binding: 2-fluoro-ara-A: ~19% to 29%
Metabolism: I.V.: Fludarabine phosphate is rapidly dephosphorylated in the plasma to 2-fluoro-ara-A (active metabolite), which subsequently enters tumor cells and is phosphorylated by deoxycytidine kinase to the active triphosphate derivative (2-fluoro-ara-ATP)
Bioavailability: Oral: 2-fluoro-ara-A: 50% to 65%
Half-life elimination: 2-fluoro-ara-A: ~20 hours
Time to peak, plasma: Oral: 1-2 hours
Excretion: Urine (60%, 23% as 2-fluoro-ara-A) within 24 hours

Dose adjustment in renal and hepatic impairment.

It appears that no adjustment is needed in hepatic impairment. Renal impairment dosing is **NOT** specific to stem cell transplant patients. In patients not receiving a stem cell transplant, doses are typically reduced by 20% for CrCl of 30-70 ml/min and not used for CrCl < 30 ml/min.

Monitoring Parameters.

CBC with differential, platelet count, AST, ALT, serum creatinine, serum albumin, uric acid; monitor for signs of infection and neurotoxicity

3.2.3. Alemtuzumab (Campath-1H)
Therapeutic Classification.
Antineoplastic Agent; Monoclonal Antibody
Pharmaceutical Data.
Injection: 30 mg/mL in phosphate buffered saline solution with disodium edetate (1 ml vial).
Stability and Storage.
Alemtuzumab vials may be stored at 2 to 8 degrees C (36 to 46 degrees F). Do not freeze, but if accidentally frozen, thaw at 2 to 8 degrees C before administration.
Use within 8 hours after dilution. Solutions may be stored at room temperature (15-30 degrees C) or

refrigerated (2 to 8 degrees C). Protect solutions from light.
No incompatibilities with polyvinylchloride (PVC) bags or PVC or polyethylene lined PVC administration sets have been observed. Admix in 100 ml of either 0.9% Sodium Chloride or 5% Dextrose.
Vial contains no preservatives and is intended for single use only. Discard vial and any unused portion after withdrawal of dose.
Administration.
Administer by I.V. infusion over 2 hours. Consider premedicating with diphenhydramine 50 mg and acetaminophen 500-1000 mg 30 minutes before initiation of infusion. Other drugs should not be added to or simultaneously infused through the same I.V. line. Do not give I.V. push.
Alemtuzumab must be filtered prior to administration. A Burron Medical 5 micron filter needle was tested and approved for such purposes; other similar filters should likewise be acceptable.
Adverse Effects.

Observed in more than 10%: Cardiovascular: Hypotension (15% to 32%), peripheral edema (13%), hypertension (11% to 15%), dysrhythmia/tachycardia/SVT (10% to 14%); Central nervous system: Fever (69% to 85%), chills (53%), fatigue (22% to 34%), headache (13% to 24%), dysthesias (15%), dizziness (12%); Dermatologic: Rash (13% to 40%), urticaria (16% to 30%), pruritus (14% to 24%); Gastrointestinal: Nausea (47% to 54%), vomiting (33% to 41%), anorexia (20%), diarrhea (10% to 22%), stomatitis/ mucositis (14%), abdominal pain (11%); Hematologic: Lymphopenia (grades 3/4: 97%), neutropenia (77% to 85%; grade 3/4: 42% to 70% [median onset: 31 days, median duration: 28-37 days]), anemia (76% to 80%; grade 3/4: 12% to 47% [median onset: 31 days, median duration 8 days]), thrombocytopenia (71% to 72%; grade 3/4: 13% to 52% [median onset: 9 days; median duration: 14-21 days]); Local: Injection site reaction (SubQ administration: 90%); Neuromuscular & skeletal: Rigors (86% to 89%), skeletal pain (24%), weakness (13%), myalgia (11%); Respiratory: Dyspnea (14% to 26%), cough (25%), bronchitis/pneumonitis (21%), pneumonia (16%), pharyngitis (12%); Miscellaneous: Infection (43% to 74%; grades 3/4: 21% to 37%; incidence is lower if prophylactic anti-infectives are utilized), CMV viremia (55%), infusion reactions (grades 3/4: 10% to 35%), diaphoresis (19%), CMV infection (6% to 16%), sepsis (15%; grades 3/4: 3% to 10%), herpes viral infections (1% to 11%)

Observed in 1% to 10%: Cardiovascular: Chest pain (10%); Central nervous system: Insomnia (10%), malaise (9%), anxiety (8%), depression (7%), temperature change sensation (5%), somnolence (5%); Dermatologic: Purpura (8%), erythema (4%); Gastrointestinal: Dyspepsia (10%), constipation (9%); Hematologic: Neutropenic fever (10%; grades 3/4: 5% to 10%), pancytopenia/marrow hypoplasia (5% to 6%; grade 3/4: 3%), positive Coombs' test without hemolysis (2%), autoimmune thrombocytopenia (2%), autoimmune hemolytic anemia (1%); Neuromuscular & skeletal: Back pain (10%), tremor (3% to 7%); Respiratory: Bronchospasm (9%), epistaxis (7%), rhinitis (7%); Miscellaneous: Moniliasis (8%)

Observed in <1%, postmarketing, and/or case reports (limited to important or life-threatening): Acidosis, acute renal failure, acute respiratory distress syndrome, agranulocytosis, alkaline phosphatase increased, allergic reactions, anaphylactoid reactions, angina pectoris, angioedema, anuria, aphasia, aplastic anemia, arrhythmia, ascites, asthma, atrial fibrillation, bacterial infection, biliary pain, bone marrow aplasia, bullous eruption, capillary fragility, cardiac arrest, cardiac failure, cardiac insufficiency, cardiomyopathy, cellulitis, cerebral hemorrhage, cerebrovascular disorder, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), coagulation abnormality, colitis, coma, COPD, coronary artery disorder, cyanosis, deep vein thrombosis, dehydration, diabetes mellitus exacerbation, disseminated intravascular coagulation (DIC), duodenal ulcer, ejection fraction decreased, endophthalmitis, Epstein-Barr virus associated lymphoproliferative disorder, esophagitis, fluid overload, flu-like syndrome, gastrointestinal hemorrhage, Goodpasture’s syndrome, Graves' disease, Guillain-Barré syndrome, hallucinations, hematemesis, hematoma, hematuria, hemolysis, hemolytic anemia, hemoptysis, hepatic failure, hepatocellular damage, HF, hyperbilirubinemia, hyper-/hypoglycemia, hyper-/hypokalemia, hypersensitivity, hyperthyroidism, hypoalbuminemia, hyponatremia, hypovolemia, hypoxia, idiopathic thrombocytopenic purpura (ITP), interstitial pneumonitis, intestinal obstruction, intestinal perforation, intracranial hemorrhage, *Legionella* pneumonia, *Listeria* meningitis, lymphadenopathy, marrow depression, melena, MI, mouth edema, myositis, optic neuropathy, osteomyelitis, pancreatitis, paralysis, paralytic ileus, paroxysmal nocturnal hemoglobinuria-like monocytes, peptic ulcer, pericarditis, peritonitis, plasma cell dyscrasia, phlebitis, pleural effusion, pleurisy,

Pneumocystis jirovecii pneumonia, pneumothorax, polymyositis, progressive multifocal leukoencephalopathy, pseudomembranous colitis, pulmonary edema, pulmonary embolism, pulmonary fibrosis, pulmonary infiltration, pure red cell aplasia, purpuric rash, renal dysfunction, respiratory alkalosis, respiratory arrest, respiratory depression, respiratory insufficiency, seizure (grand mal), serum sickness, sinus bradycardia, splenic infarction, splenomegaly, stridor, subarachnoid hemorrhage, syncope, toxic nephropathy, thrombocythemia, thrombophlebitis, throat tightness, transfusion-associated GvHD, tuberculosis, tumor lysis syndrome, ureteric obstruction, urinary retention, urinary tract infection, ventricular arrhythmia, ventricular tachycardia, viral meningitis, virus reactivation (latent)
Mechanism of Action.
Binds to CD52, a nonmodulating antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. After binding to CD52+ cells, an antibody-dependent lysis of leukemic cells occurs.
Human Pharmacology.

Distribution: Vd: I.V: 0.1-0.4 L/kg
Metabolism: Clearance decreases with repeated dosing (due to loss of CD52 receptors in periphery), resulting in a sevenfold increase in AUC.
Half-life elimination: I.V.: 11 hours (following first 30 mg dose; range: 2-32 hours); 6 days (following the last 30 mg dose; range: 1-14 days)
Dose adjustment in renal and hepatic impairment.
It appears no dose adjusted are needed in renal or hepatic impairment.
Monitoring Parameters.
Vital signs; carefully monitor BP especially in patient with ischemic heart disease or on antihypertensive medications; CBC with differential and platelets (weekly, more frequent if worsening); signs and symptoms of infection; CD4+ lymphocyte counts (after treatment until recovery); CMV antigen (every 1-2 weeks). Monitor closely for infusion reactions (including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash).

4.0 Patient Eligibility

Inclusion Criteria:

1. Age >/= 18 years and </= 65 years.
2. One of the following:
   a. Acute leukemia past first remission, in first or subsequent relapse, in second or greater remission. Patients in first remission should have with intermediate or high cytogenetic risk factors or flt3 mutation. Patients with relapsed disease. Patients with primary induction failure or relapse are eligible if they have < 10% bone marrow blasts, and no circulating blasts.
   b. Myelodysplastic syndrome with intermediate or high risk IPSS score, or treatment related MDS.
   c. CML resistant or intolerant to tyrosine kinase treatment in a first or subsequent chronic phase or after transformation to accelerated phase or blast crisis.
   d. CLL, Lymphoma or Hodgkin's disease which has failed to achieve remission or recurred following initial chemotherapy. Patients must have at least a PR to salvage therapy, or low bulk untreated relapse (< 2 cm largest mass).
   e. Multiple myeloma which has relapsed or progressed and has achieved a partial response to salvage chemotherapy.
3. Patients must have one of the following donor types identified who are willing to donate peripheral blood:
   a. Related donor, 8/8 HLA-matched for HLA-A, -B, C and DR matched or,
   b. Matched Unrelated Donor (MUD), 8/8 HLA-matched for HLA A, B, C and DRB1 using allele level typing.
4. Performance score of at least 80% by Karnofsky.
5. Adequate major organ system function as demonstrated by:
   a. Creatinine < 1.8 mg/dl (or creatinine clearance > 40 ml/min)
   b. Bilirubin < 1.5 mg/dl except for Gilbert's disease

c. ALT < 300 IU/ml
d. Left ventricular ejection fraction equal or greater than 40%.
e. Pulmonary function test (PFT) demonstrating a diffusion capacity of least 50% predicted, corrected for hemoglobin.

6. Patient or patient's legal representative, able to sign informed consent.
7. Patient or patient's legal representative, parent(s) or guardian able to provide written informed consent for the long-term follow-up gene therapy study 2006-0676.
8. The patient will need to be available for evaluation within 72 hours of symptoms of GVHD, occurring within 60 days of the planned donor lymphocyte infusion.

Exclusion Criteria:

1. Uncontrolled active infection.
2. Positive Beta HCG test in a woman with child bearing potential, defined as not post-menopausal for 12 months or no previous surgical sterilization.
3. Women of child bearing potential not willing to use an effective contraceptive measure while on study.
4. Men not willing to use an effective contraceptive measure while on study.
5. Known sensitivity to any of the products that will be administered during the study.
6. HIV seropositive.
7. Prior allogeneic transplant.

5.0 Criteria to Receive DLI

At approximately 60 days post transplant patients will be eligible to receive the DLI infusion if they meet the following criteria:

1. Patient must be off Tacrolimus for at least one week.
2. No evidence of grade >2 GvHD following HSCT.
3. Not requiring corticosteroid treatment methylprednisolone > 16 mg/day for any reason.
4. Recovery of (ANC) > 1000 neutrophils/mcL.
5. Recovery of platelets >20,000/mcl and independent of platelet transfusion.
6. > 25% donor T-cell chimerism in peripheral blood, obtained after day 21 post transplant.
7. Performance score of at least 80% by Karnofsky.
8. No uncontrolled infections or active toxicities > grade 3.
9. Creatinine < 2 mg/dl.
10. Bilirubin <2 mg/dl, and SGOT < 200 mg/dl).
11. No progression of malignancy requiring alternative treatment.
12. The product must have completed final release testing and a certificate of analysis issued by the Bellicum Corporation. This study will utilize a single dose of 3 $x10^6$ T-cells/Kg T-cells. Patients who do not meet these criteria will discontinue the study and will be followed up per routine standard of practice for patient receiving stem cell transplant.

6.0 Treatment Plan

The proposed treatment plan of this study has two components. The first component is the stem cell transplant which is carried out using standard preparative regimen; the second component, which is the actual investigation is the planned DLI infusion. The transplant day is referred to as day zero (D0), treatment plan activities prior or after D0 are denoted as day minus (D-) or day plus (D+).

Patients will receive standard reduced intensity regimen using fludarabine, melphalan, and alemtuzumab to achieve engraftment with a low risk of GVHD. At approximately 60 days post transplant patients who are alive and without GVHD will receive DLI to enhance graft-vs.-malignancy and immune reconstitution.

The goal is to administer more than 3 x 10^6 CD34+ cells/kg of peripheral blood progenitor cells (PBPC) collected from a HLA compatible related or unrelated donor. The PBPC can be administered either fresh or after cryopreservation. A fraction of this product containing at least 1X10^9 CD3 positive cells will be

separately cryopreserved for use in the manufacture of the gene-modified T cell DLI.

In the unlikely event that insufficient cells are available to set aside the planned DLI, or if the DLI cannot be effectively cryopreserved, the donor may be asked to subsequently donate a DLI by a separate leukapheresis.

6.1 Preparative regimen

6.1.1 D-6 to D-3 Fludarabine administration:

Fludarabine is administered IV at the dose of 40 mg/m^2 in 100 ml of normal saline on each of four (4) consecutive days. Fludarabine will be dosed per actual body weight/actual body surface area.

6.1.2 D-2 Melphalan administration:

Melphalan is administrated IV at the dose of 140 mg/m^2. Melphalan will be dosed per actual body weight/actual body surface area for patients less than or equal to 20% over their Ideal Body Weight (IBW). For patients greater than 20% over IBW, an adjusted body weight will be utilized to calculate the body surface area with the following calculation:

Adjusted body weight (kg)= (Actual weight (kg) + IBW (kg)) / 2

6.1.3 D-1 Alemtuzumab administration:

Alemtuzumab is be given as a flat dose of 50 mg IV on D-1. It will be prepared in 100 ml NS or 5% Dextrose and administered by a controlled rate pump. To prevent infusion reactions, patients should receive premedications including diphenhydramine 50 mg IV and hydrocortisone 150 mg IV.

6.2 D0 Stem Cell infusion:

Fresh or cryopreserved peripheral blood progenitor cells will be infused.

6.3 Between D+1 and D+45

GvHD with Tacrolimus and Mini Methotrexate with dose adjustment as clinically indicated. Tacrolimus will be administered at starting dose of 0.015 mg/kg (ideal body weight) as a 24 hour continuous infusion daily adjusted to achieve a therapeutic level of 5-15 ng/ml (target is 10 ng/ml). Tacrolimus is changed to oral dosing when tolerated. Methotrexate 5 mg/m2 will be dosed based on actual body surface area and administered intravenously on days +1, +3, +6, and +11. Tacrolimus tapering should start on approximately D+35 with the intention for the patient to be completely off the drug by approximately Day +45.

G-CSF administered at a dose of 5 mcg/kg/day (rounded up the nearest vial size) subcutaneously beginning on D+7, and continuing until the absolute neutrophil count (ANC) is > 500 x 10/L for 3 consecutive days.

Doses of these medications may be modified by the attending physician as clinically indicated.

Prophylactic and therapeutic antibiotics should be given according to Stem Cell Transplantation & Cellular Therapy standard practices

6.4 Between D+56 and D+64:

Planned Donor Lymphocyte Infusion (DLI) either as fresh or cryopreserved donor peripheral blood mononuclear cells.

Patients who meet the criteria for continuing on study post HSCT may receive a planned DLI infusion iCasp9 (BPZ-1001)-Modified T-cells) of 3 X 10^6/kg in 100 ml infused over approximately a one hour period between day +56 to day+64. Patients with intercurrent medical problems which preclude treatment within this interval, the DLI may be frozen and stored for infusion up to 6 months post transplant. Vital signs will be checked at approximately 30 minutes after completion of the infusion.

Patient will receive premedication with Benadryl 25 mg IV and acetaminophen 650 mg PO. Corticosteroids are not administered as a premedication.

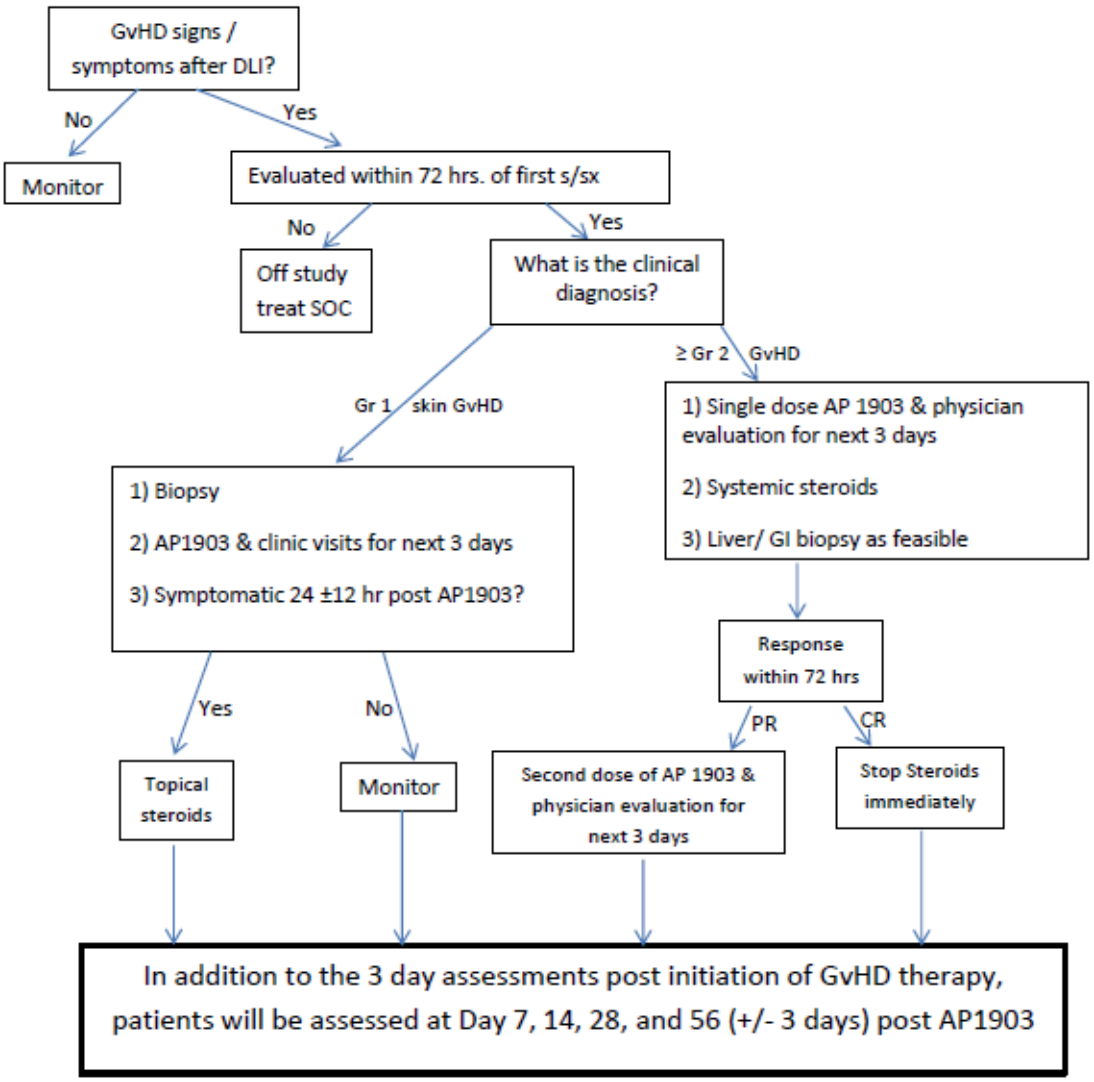
Patients on this protocol receive a single infusion of the iCasp9 (BPZ-1001)-Modified T-cells. Any remaining cells are used for correlative scientific studies.

Evaluation and treatment of patients developing acute GVHD after the BPZ-1001 modified T-cell infusion.
Patients must be evaluated within the first 72 hours of the first signs and or symptoms of suspected acute GvHD prior to start treatment with AP1903 +/-steroids. The evaluation includes clinical assessment and biopsy when possible.

Those patients who are no longer geographically proximate to the trial site and cannot return within 72 hours of suspected GvHD will be taken off study and receive treatment as per standard practice.

Biopsy of involved tissue is strongly encouraged, but not required for initiation of GvHD therapy with AP1903. Only a clinical diagnosis of acute GvHD is necessary for initiation of GvHD therapy with AP1903.

GvHD Treatment with AP1903 ± steroids.



For patients that present with a clinical diagnosis of grade I GvHD, a skin biopsy should be performed prior to administration of a single dose of AP1903 (0.4 mg/kg as an intravenous infusion over approximately 2 hours). The AP1903 dose is based on published Pk data which show plasma concentrations of 10-1275 ng/mL over the 0.01 mg/kg to 1.0 mg/kg dose range with plasma levels falling to 18% and 7% of maximum at 0.5 and 2hrs post dose.[58] Responses have been rapid in the initial studies of this approach, occurring within the first 24-48 hours. After 24 ($\pm$ 12) hours post AP1903 infusion, those patients who remain symptomatic with a rash will start topical steroids (topical 0.1% triamcinolone cream or 1% hydrocortisone cream for facial rash 3 times daily). Those patients whose rash is asymptomatic will not start topical or systemic steroids.

For patients with a clinical diagnosis of grade $\geq$ 2 GvHD, a single dose of AP1903 (0.4 mg/kg as an intravenous infusion over approximately 2 hours) will be administered. After completion of the AP1903 infusion, systemic steroids will be initiated according to the schedule recommendations given below. If needed, a second dose of AP1903 may be infused 24-72 hours after the first AP1903 infusion. Liver/GI biopsies will be obtained as quickly as possible thereafter if considered clinically feasible by the attending physician.

Once treatment with AP1903 ± steroids begins, patients will be seen by a physician for assessment of GVHD every day for the next 3 days. Patients who do not experience a CR within 72 hours may receive a second dose of AP1903, and assessed daily for 3 days for assessment of GvHD. In addition to the 3 day assessments post initiation of GvHD therapy, patients will be assessed at Day 7, 14, 28 and 56 post AP1903. Assessments may be performed ± 3 days of scheduled dates.

For a patient whom has a recurrence of GVHD, or a new occurrence in the same or different organ, AP1903 may be administered per the Study Chair's discretion.

Treatment with systemic steroids.
Patients beginning systemic steroids will receive methylprednisolone 1.6 mg/kg per day intravenously (or prednisone 2 mg/kg per day orally) divided in 2 to 3 daily doses. Patients who GvHD resolve as defined by a CR within 72 hours would have steroids stopped immediately.

Patients who fail to achieve a CR within 72 hours of an initial dose of AP1903, or within 48 hours of a second dose of AP1903, will be maintained on this dose for no less than 7 days. Steroids can then be tapered as tolerated to no less than methylprednisolone 0.2 mg/kg per day (or prednisone 0.25 mg/kg per day) at day 28. A suggested steroid taper schedule is provided below; however, adherence will be optional apart from days 7 and 28 stipulations.

If acute GvHD progresses within 3 days or no response by 14 days, then treat with alternative systemic secondary GvHD therapy at the physician's discretion. This patient would be considered a failure for the primary endpoint. This patient will be considered "off study treatment", but will remain on study to be followed for study endpoints.

Patients who achieved a day 28 CR and have a subsequent flare of aGvHD can receive alternative agents at the treating physician's discretion or, alternatively, receive a temporary increase in the dose of steroids.

6.5 Use of Other Investigational Agents
Other investigational agents may not be administered from the time of HSCT through 60 days post the T cell infusion.

6.6 Corticosteroids Dosing and Taper
Patients receiving full dose corticosteroids for less than 3 days who experience a complete response will have steroids discontinued. On the 4th day of full dose corticosteroids, steroids will be tapered as tolerated according to suggested schedule or to standard practices, but to no less than 0.2 mg/kg/day methylprednisolone (or prednisone 0.25 mg/kg/day) on Day 28. Then continue tapering with a goal to reach less than 0.16 mg/per/kg per day of methylprednisolone (or less than 0.2 mg/per/kg per day of prednisone) Day 56.

Steroid taper may also start if GvHD is improving. Improvement is defined as any clinically recognizable lessening of skin rash, redness, or extent; lessening of diarrhea or lowered bilirubin (though it does not have to be greater than or equal to one stage improvement in any involved organ), without worsening in any organ.

Table 2 Suggested Taper for Responders to Systemic Steroid Therapy.

Dose Amount	Frequency	Days
2 mg/kg/day of prednisone orally (or 1.6 mg/kg/day of methylprednisolone I.V) divided	Once or twice/day	Days 1-7
1.5 mg/kg/day	Once daily	Days 8-10
1 mg/kg/day	Once daily	Days 11-15
0.5 mg/kg/day	Once daily	Days 16-20
0.25 mg/kg/day	Once daily	Days 21-28

If acute GvHD flares after termination of prednisone, or during taper of prednisone, steroid dosing may be re-escalated or secondary therapy added at the discretion of the treating physician. Re-escalation of steroid for GvHD flare alone will not be considered as treatment failure.

6.7 Topical and Ancillary GvHD Therapies:

Topical therapy for acute GvHD, including skin creams or GI non-absorbable steroids are allowed and should be used according to standard practices. Use of topical agents for management of acute GvHD will be recorded as a secondary endpoint assessment in this trial.

Ancillary/supportive care measures for acute GvHD such as the use of anti-motility agents for diarrhea, including octreotide, is allowed at the discretion of the treating physician. Use of ursodiol to prevent/ reduce gall bladder sludging, or prevent hepatic transplant complications is also allowed according to standard guidelines.

7.0 Study Evaluations

Evaluation Prior to Transplant (baseline).
Standard work up for transplant as well as disease assessment is done prior to study entry as part of diagnostic or routine pre-transplant evaluation.

Prior to Planned Donor Lymphocyte Infusion

Following the HSCT and prior to DLI, the subject will undergo the following evaluations to assess their status and determine eligibility to receive the planned DLI:

Physical examination and adverse event documentation including GvHD assessment.
Assessment for infections
Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells.
Bone marrow aspiration and biopsy, with cytogenetics if clinically indicated.
Complete blood count (CBC), differential and platelets.
Serum creatinine and bilirubin and SGOT.

Post Planned Donor Lymphocyte Infusion (DLI)
Patients will be evaluated approximately twice weekly according to standard of care practice until approximately 60 days following the DLI. Thereafter at approximately 180 days and at 1 year following the hematopoietic stem cell transplant.

If clinically indicated these visits may be done at other time points which can replace the nearest planned time-point.

1. The following lists the minimum evaluations required:

Physical examination and adverse event documentation including GvHD assessment.
Occurrence of infections.
Occurrence of post-transplant lymphoproliferative disorder (PTLD)
Complete blood count (CBC), differential and platelets.
Serum creatinine and bilirubin and SGOT.
CMV polymerase chain reaction (PCR) of antigenemia assay (performed approximately weekly).

For patients receiving AP1903 for treatment of GVHD, the following blood samples will be obtained to detect the BPZ-1001 modified T-cells and determine if they are eliminated by the AP1903 treatment: Within 3 hours prior to AP1903 infusion, approximately 2 hours post AP1903 infusion, and approximately 24 hours (+/- 5 hours) post AP1903 infusion. Forty (40) ml of blood will be collected at each time point. Thirty (30) ml will be sent to Bellicum laboratories, and 10 ml will be sent to Dr. Katy Rezvani's laboratory at MD Anderson.

2. If clinically indicated,

Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells.

Bone marrow aspiration and biopsy, with cytogenetics.

Immune Reconstitution Studies
Depending on availability of patient cells and reagents, immune reconstitution studies (Immunophenotyping, T and B cell function): blood (40 ml each time) will be obtained at approximately the following intervals: Prior to DLI infusion, then 4 hours after the DLI infusion, once a week for 4 weeks, at approximately 6 weeks, and then at approximately 2, 3, 6, 9 and 12 months post DLI). Samples may be collected +/-3 days of the scheduled dates for the first 2 months, and +/- 2 weeks for the later samples).

Several parameters will be analyzed to measure immune reconstitution resulting from iCaspase9-transduced T-cells. These include repeated measurements of total lymphocyte counts, CD3+ T and CD19+ B cell numbers, and FACS analysis of T cell subsets (CD3, CD4, CD8, CD16, CD19, CD25, CD27, CD28, CD45RA/RO, CD56, CD62L, CD69, CD80, CD86, CCR7, HLA-DR). Approximately 10-60 ml of patient blood will be taken, if feasible, and sent to Bellicum laboratories (Houston, Texas). The amount of blood taken will be dependent on the size of the recipient and will not exceed 1-2 cc/kg in total (allowing for blood taken for clinical care and study evaluation) at any one blood draw. These studies will be performed in the MD Anderson Stem Cell Transplantation and Cellular Therapy (SCTCT) research laboratory in Houston, Texas.

Samples permitting, additional research studies may be performed in the SCTCT research laboratory focused on T cell functional activity such as T cell repertoire analysis, antiviral and antitumor reactivity.

Persistence and safety of transduced T-cells (RCR)
Prior to DLI infusion, then at approximately 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 months post DLI, then yearly starting at 5 years post DLI for 10 years (20 ml each time): Phenotype to detect the presence of transgenic cells. Samples for RCR testing will be sent to Bellicum (Houston, Texas) and assayed or archived as per the FDA guidelines. Samples may be collected +/-3 days of the scheduled dates for the first month and +/- 2 weeks for the later samples).

HAMA
One ten (10) mL serum sample at baseline and approximately 3 months post DLI (+/- 2 weeks).

M.D. Anderson Symptom Inventory (MDASI)
Study partipants who are able to communicate in English will complete the MDASI by traditional paper and pencil method or through a telephone interview with the research staff at enrollment, at the time of DLI, at the occurence of GVHD before receiving AP1903, and approximately 7 and 14 days after receiving AP1903. Partipants who do not develop GVHD post DLI will complete the questionnaire approximately one month later.

Long-Term Follow-Up
Enrolled research participants who receive engineered T cells will be asked to participate in long-term follow-up (LTFU) per the guidelines set forth by the FDA's Biologic Response Modifiers Advisory Committee (BRMAC) that apply to gene transfer studies. Current recommendations from the FDA require a minimum of 15 years of follow-up after infusion of genetically modified cells. Since the long-term effects of gene therapy are unknown, the research participant, after receiving a T-cell infusion, will be required to participate in MDACC IRB study for LTFU of gene therapy patients (IRB # 2006-0676) and sign the associated consent form. During follow-up, research participants will not be considered as participants in retroviral studies, and blood will not be sent for testing of replication competent retrovirus (RCR). If the research participant dies, an autopsy may be requested, but is not mandatory.

8.0 GvHD Scoring

GvHD developed after the planned donor lymphocyte infusion will be scored as below. Patients will be assessed and GvHD will be scored daily for the first 3 days and then at each visit.

Acute GvHD: Staging and Grading

Table 1. Modified Keystone Staging

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash < 25% BSA	25-50%	> 50% Generalized erythroderma	Plus bullae and desquamation
Gut	Adult: < 500 ml/day Child: < 10 ml/kg/day	Adult: 500-1000 ml/day Child: 10-19.9 ml/kg/day	Adult: 1001-1500 ml/day Child: 20-30 ml/kg/day	Adult: >1500 ml/day Child: > 30 ml/kg/day	Severe abdominal pain +/- ileus, frank blood or melena
UGI		Severe nausea/vomiting			
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	>15mg/dl

Table 2. Grading Schema

	Skin	Liver	Gut	Upper GI
0	None and	None and	None and	None
I	Stage 1-2 and	None and	None	None
II	Stage 3 and/or	Stage 1 and/or	Stage 1 and/or	Stage 1
III	None-Stage 3 with	Stage 2-3 or	Stage 2-4	N/A
IV	Stage 4 or	Stage 4	N/A	N/A

Response Definitions:
Complete response (CR): is defined as score of 0 for the GvHD grading in all evaluable organs.

For a response to be scored as CR at Day 56 or later, the patient must still be in CR on that day and have had no intervening additional therapy for an earlier progression, PR or NR.

Partial response (PR): is defined as improvement in one or more organs involved with GvHD symptoms without progression in others.

For a response to be scored as PR at Day 28 or later, the participant must still be in PR on that

day and have had no intervening additional therapy for an earlier progression, PR or no response (NR).

Mixed response (MR): is defined as improvement in one or more organs with deterioration in another organ manifesting symptoms of GvHD or development of symptoms of GvHD in a new organ.

Progression of GvHD (PD): is defined as deterioration in at least one organ without any improvement in others.

No response (NR): is defined as absence of any improvement or progression as defined. Patients receiving secondary therapy (including need to re-escalate steroid dose to > 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) will be classified as non-responders.

GvHD Flares: are defined as any progression of acute GvHD after an initial response (i.e., earlier CR or PR) that requires re-escalation of steroid dosing, or initiation of additional topical or systemic therapy.

Chronic GvHD (CGvHD)
If CGvHD developed after the planned donor lymphocyte infusion will be scored as below.

Definite and Possible Manifestations of Chronic GvHD*

Organ System	Definite manifestations of chronic GvHD	Possible manifestations of chronic GvHD
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
GI tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia
GU	Vaginal stricture, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculoskeletal/ Serosa	Non-septic arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias

Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis

*From BMT CTN MOP Chapter 2

9.0 Scoring of Secondary Objectives

Scoring of Secondary Endpoints:

9.1.1.1 Disease-Free Survival at 6 Months Post Enrollment:
Disease-free survival at 6 months will be computed. The events for disease-free survival are death and relapse of the underlying malignancy.

9.1.1.2 Non-relapse Mortality at 6 Months Enrollment:
Non-relapse mortality at 6 will be computed for each treatment arm.

9.1.1.3 Overall and GvHD-free Survival:
Overall survival and GvHD-free survival at Day 180 will be computed.

9.1.1.4 Systemic Infections through Day 180:
All microbiologically documented infections or significant infections requiring antibiotic/antifungal therapy occurring within six months of initiation of therapy will be reported by site of disease, date of onset, and severity. For definitions see the BMT CTN MOP.

9.1.1.5 Proportion of Patients Requiring a 7 Day Hospitalization post DLI and post Administration of AP1903.

9.1.1.6 Incidence of EBV:
Participating sites are to collect any incidence of EBV-associated lymphoproliferative disorder or EBV reactivation requiring therapy though Day 180.

9.1.1.7 Proportion of Patients Developing Gr I-IV acute GvHD and chronic GvHD by Day 28, 56 and 180 post DLI.

9.1.1.8 Proportion of CR, PR, MR, NR and PD:
At Days 3, 7, 14, 28 and 56, scoring of CR, PR, MR, NR and PD are in comparison to the participant's acute GvHD status (score) on the day that GvHD is ascertained but prior to administration of AP1903.

9.1.1.9 Proportion of Primary Treatment Failures:
Proportion of primary treatment failures among surviving patients at Days 3, 7, 14, 28 and 56. No response, progression, administration of additional systemic therapy for GvHD (or re-escalation of steroid dose to > 2.5 mg/kg/day of prednisone (or methylprednisolone equivalent of 2 mg/kg/day), or mortality by Day 3, 7, 14, 28 or 56 post-initiation of treatment will be considered a primary treatment failure.

9.1.1.10 GvHD Flares: Requiring Additional Therapy:
Flares are defined as any progression of acute GvHD after an initial response (i.e., earlier CR or PR) that requires re-escalation of steroid dosing, or initiation of additional topical or systemic therapy. While all "flares" will be captured, only flares that require additional systemic therapy (that is additional drugs) or re-escalation of steroids to > 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day] will be counted as failure for the primary endpoint. The rate of all flares before Day 90 will be examined as a secondary endpoint.

9.1.1.11 Chronic GvHD (CGvHD): If CGvHD developed Immunosuppression Discontinuation:
Discontinuation of immunosuppression will be assessed by Day 3, 7, 14, 28, 56, and 180. The date of

discontinuation of corticosteroids will be recorded. In addition, dates for discontinuation of all other systemic immunosuppressive medications (where applicable), including cyclosporine or tacrolimus, sirolimus, etc. for treatment or prevention of acute GvHD will be captured.

9.1.1.12 Steroid Use at Days 3, 7, 14, 28 and 56 after AP1903:
Doses of methylprednisolone will be converted to prednisone equivalents by multiplying the planned donor lymphocyte infusionmethylprednisolone dose by 1.25. Prednisone doses for each patient will be converted to mg/kg. The cumulative prednisone dose for each patient at Day 28 and 56 will be calculated by adding the doses (end of each week's dose) for each of the first four weeks of treatment, divided by the number of days of survival during this interval. The prednisone dose for each patient at 3, 7, 14, 28, and Day 56 will be recorded

9.1.1.13 Incidence of Topical/Non-absorbable Therapy by Day 56 after AP1903:
The proportion of patients using either topical skin or topical GI steroids will be calculated.

9.1.1.14 Change in Patient-reported Outcomes:
Study partipants who are able to communicate in English will complete the M.D. Anderson Symptom Inventory (MDASI) by traditional paper and pencil method or through a telephone interview with the research staff at enrollment, at the time of DLI, at the occurence of GVHD before receiving AP1903, and approximately 7 and 14 days after receiving AP1903. Partipants who do not develop GVHD post DLI will complete the questionnaire approximately one month later. The MDASI is a 19 item instrument that captures 13 symptoms (0="not present" to 10="as bad as you can imagine") and 6 items measuring interference with life from 0 ("did not interfere") to 10 ("interfered completely"). See the MDASI in Appendix E. It provides two summary scales: symptoms and interference. The MDASI will be scored according to the recommendations of the developers. We estimate it will take 5 minutes to complete the MDASI. Surveys are completed by participants using self-completed instruments as a first choice. If this method of data collection is not possible, then surveys and response options may be read verbatim to participants, either in person or over the phone, to collect data. Although the MDASI has been psychometrically validated in 8 languages, including Spanish, given the exploratory nature of this endpoint we will only administer the MDASI to patients who are able to communicate in English. Surveys may not be completed by surrogates.

9.1.1.15 Chronic GvHD:
The incidence of chronic GvHD at 6 months will be computed for each treatment arm.

10.0 Study Definitions

Active treatment administration is defined as the DLI infusion.

Active treatment period is defined as from the completion of the DLI infusion through D+60.

Follow-up period is defined as from D+61 until one year of treatment completion.

Engraftment is defined as the evidence of donor derived cells (more than 95%) by chimerism studies in the presence of neutrophil recovery by day 28 post stem cell infusion.

Other definitions used to assess engraftment:

Neutrophil recovery is defined as a sustained absolute neutrophil count (ANC) > 0.5 x 10^9/L for 3 consecutive days.

Engraftment date is the first day of three (3) consecutive days that the ANC exceeds 0.5 x10^9/L.

Delayed engraftment is defined as the evidence of engraftment beyond day 28 post SC infusion achieved after the administration of therapeutic (high dose) hematopoietic growth factors.

Primary Graft failure is defined as failure to achieve an ANC > 0.5 x 10^9/L for 3 consecutive days by day 28 post SC infusion, with no evidence of donor derived cells by bone marrow chimerism studies and no evidence of persistent or relapsing disease.

Secondary graft failure is defined as a sustained declined of ANC <0.5 x 10^9/L for 3 consecutive days after initial documented engraftment with no evidence of disease progression.

Autologous reconstitution is defined by the presence of ANC > 0.5 x 10^9/L without evidence of donor-derive cells by bone marrow chimerism studies. This can occur at initial engraftment or later after initial engraftment has been documented.

Disease Response as per CIBMTR criteria.

A. For AML/MDS:

Complete remission (CR):
BM < 5% blasts (absence of blasts with Auer rods).
ANC > 1000/ul.
Platelet count >100 x 10e9/ul (independent of red cell transfusions).
Absence of extramedullary disease.

Marrow CR (CRi) (incomplete hematologic recovery).
BM < 5% blasts (absence of blasts with Auer rods).
ANC < 1000/ul or Platelet count <100 x 10e9/ul.
Absence of extramedullary disease.

No Response (NR) or Disease Progression
BM > 5% leukemia blasts
Persistent presence of blasts in peripheral blood.
Presence of extramedullary disease.

B. For CML:

Cytogenetic Response
Complete: No Ph positive metaphases.
Major: 0-35% Ph positive metaphases.
Partial: 1-34% Ph positive metaphases.
Minor: 35-90% Ph positive metaphases.

Complete Hematologic Response
Complete normalization of peripheral blood counts with leukocyte count <10x10^9/L.
Platelet count <450x10^9/L.
No immature cells in peripheral blood.
No signs and symptoms of disease with disappearance of palpable splenomegaly.

Partial Hematologic Response
Same as complete hematologic response, except for:
Presence of immature cells.
Platelet count < 50% of the pretreatment count, but >450x10^9/L.
Persistent splenomegaly, but < 50% of the pretreatment extent.

Molecular Response:
Complete molecular response: BCR-ABL mRNA undetectable by RT-PCR.
Major molecular response equal or more 3-log reduction of BCR-ABL mRNA.

C. For CLL:

Complete Response (CR):
No lymphadenopathy; no organomegaly.
Neutrophils >1.5 x10^9/L; platelets >100 x10^9/L; Hg > 11g/dL, lymphocytes;
Absence of constitutional symptoms.

Nodular Partial Response (NPR):
CR with persistent lymphoid nodules in the bone marrow.

Partial Response (PR):
Equal or more than 50% decrease in peripheral blood lymphocytes count from pre-pre-treatment value.
Equal or more than 50% reduction in lymphadenopathy, liver and or spleen if abnormal at pre-treatment.
50% reduction from baseline in one or more of the following: Neutrophils, platelets, Hg and lymphocytes.

Stable Disease (SD):
No change in disease status from baseline, no progression.

Disease Progression:
More than 50% increase in one or more of the following:
The sum of the products of 2 or more lymph nodes or new nodes; the size of liver, spleen, in absolute lymphocyte count;
New hepatomegaly or splenomegaly.
Transformation to a more aggressive histology.

D. For Multiple Myeloma

Stringent complete response (sCR) (all of the following):
CR as defined.
Normal free light chain ratio
Absence of clonal cells in bone marrow by inmmunohistochemistry or immunofluorescence (defined by
absence of abnormal kappa/lambda light chain ratio of >4:1 or <1:2).

Complete response (CR) (all of the following):
Negative immunofixation in serum and urine.
Less than 5% plasma cells in the bone marrow.
Disappearance of any soft tissue plasmacytomas.

Very good partial response (VGPR) (one of the following):
Serum and urine M protein detectable by immunofixation but not by electrophoresis.
90% or greater reduction in serum M protein plus urine M protein level <100 mg per 4h.

Partial response (PR) (all of the following):
Reduction by > 50% in serum monoclonal protein.
Reduction of urinary monoclonal protein to < 200 mg/24h or >90%.

Stable disease:
Not meeting criteria for CR, VGPR, PR or PD.

Progressive disease (PD) (any one or more of the following):
Increase of >= 25% from baseline in:
Serum M protein (absolute increase must be >= 0.5 g/dL).
Urine M component (absolute increase must be >= 200 mg/24h).Only in patients without measurable serum and urine M protein levels.
Difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL).
Bone marrow plasma percentage (absolute % must be >=10%).

Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mol/L) that can be solely
attributed to the myeloma.

Relapse from CR (any one or more of the following):
Reappearance of serum or urine M protein by immunofixation or electrophoresis.
Development >=5% plasma cells in the bone marrow.
Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion or hypercalcemia).

Non-relapse mortality (NRM) is defined as death from any cause other than relapse disease.

Disease free survival (DFS) is defined as the interval between day of transplant and day of death or disease progression.

Overall Survival (OS) is defined as the interval between day of transplant and day of death.

Off Study Criteria:
1. If the donor harvest of T-cells provides inadequate number of T-cells for subsequent cell processing and it if it is not possible to obtain the required additional T-cells. The minimum number of T-cells collected must be at least 10^9 T-cells.
2. Patient withdrawal of consent.
3. Unexpected pattern of toxicity.
4. An adverse event, inter-current illness or laboratory abnormality may justify a subject's removal from the study, if in the opinion of the investigator this is justified.
5. Treatment with other investigational agent.
6. Patient non-compliance with study treatment plan.
7. Pregnancy.
8. Disease progression.
9. Lost to follow-up.
10. Unable to be evaluated within 72 hours of suspected GvHD.
11. Not meeting the criteria to received DLI infusion.

11.0 Adverse Events Scoring and Reporting

Adverse events (event name, grade, start/stop date, and attribution) will be documented in the medical record and entered into CORe/PDMS. CORe/PDMS will be used as the electronic case report form for this protocol. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Assessment of the Adverse Events Severity.

The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.0 (CTCAE).

Events not included in the CTCAE chart will be scored as follows:

General grading:
Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life Threatening: discomfort that represents immediate risk of death

Grading for specific syndromes:
Veno-occlusive disease (VOD):

Grade 3: Bili >2mg/dl with at least two of the following: increased weight >4% from baseline, ascites or hepatomegaly
Grade 4: pulmonary and or renal failure

Pulmonary events not caused by CHF (interstitial pneumonitis (IP), pulmonary hemorrhage (DAH):
Grade 1: CXR showing mild infiltrates or interstitial changes
Grade 2: mild SOB
Grade 3: requires supplemental oxygen, or is a documented infection
Grade 4: requires intubation

Transplant related microangiopathy:
Grade 1: No treatment required
Grade 2:Requires steroids and/or plasma transfusions
Grade 3: Requires plasma exchange

Cytokine storm or engraftment syndrome:
Grade 1: No treatment required
Grade 2: Treatment required
Grade 3: Organ dysfunction
Grade 4: Total Bilirubin >5

Hemorrhagic Cystitis:
Grade 1: minimal or microscopic bleeding/pain
Grade 2: gross bleeding/pain and spasms
Grade 3: transfusion/irrigation required
Grade 4: dialysis required

Casuality Assessment.
The investigational component of the treatment plan of this study is the infusion of DLI post transplant. Allogeneic stem cell transplantation with Fludarabine/Melphalan reduced intensity regimen (Allo Flu-Mel) is considered standard of care and their associated adverse events are well known. Therefore, for the purpose of this study when, in the presence of an adverse event which a direct relationship to the DLI infusion is suspected, the event will be attributed to the DLI infusion.

Events caused by Allo Flu-Mel and its direct consequences as well as those events known to be related to drugs used for supportive care, prophylaxis of GvHD and infections will be scored as unrelated to the DLI infusion.

The principal investigator will be the final arbiter in determining the casuality assessment.

List of most common expected adverse events.
1. Infections in the presence or absence of neutropenia: fungal, bacterial and or viral infections.
2. Fever: Non-neutropenic or neutropenic without infection
3. Acute graft versus host disease (aGvHD): most commonly manifested by skin rash, diarrhea and abnormal liver function tests could also present with some degree of fever, upper gastrointestinal symptoms (nausea and vomiting) mucositis and eye dryness.
4. Gastrointestinal (GI tract): the GI tract manifestations could be not only due to direct damage from the preparative regiment but also be a manifestation of GvHD or infections. Therefore, the time course and its presentation are crucial when assessing these as adverse events. Nausea/vomiting, mucositis, diarrhea when presented within first 7 to 10 days most likely will be related to the preparative regimen.
5. Skin rash: not related to GvHD could be caused by chemotherapy used for the preparative regimen or antibiotics used a supportive treatment.
6. Transaminitis: liver function test elevation.
7. Pulmonary events: not related to CHF most likely caused by drug injury or infection. These could present with a pneumonitis pattern manifested with shortness of breath, pulmonary infiltrates on

chest radiograph, sometimes accompanied by fever and cough and progress to acute respiratory insufficiency and a diffuse bilateral alveolar pattern.

8. Cytokine Storm/ engraftment syndrome: most likely caused by released cytokines.
9. Hemorrhagic cystitis: not related to chemotherapy agents used in the proposed preparative regimen is most likely caused by viral infection.
10. Thrombotic thrombocytopenic purpura (TTP).
11. Veno-occlusive Disease of the Liver (VOD): could be caused by busulfan. Some antimicrobial agents have been also incriminated in its development.
12. Fluid overload due to hydration required for conditioning regimen, blood product transfusions and or IV alimentation
13. Graft failure.
14. Chronic GvHD.
15. For the purpose of this study the following events would not be considered adverse events and would not be recorded in the database:
    1. Flu-like symptoms not associated with infection
    2. Abnormal laboratory findings considered associated to the original disease
    3. Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of ALT, AST, LDH and alkaline phosphatase.

Adverse events considered serious.

1. Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation).
2. Readmissions from any cause resulting in a prolonged hospitalization (>10 days).
3. Graft Failure/ rejection.
4. Any expected or unexpected event resulting in an irreversible condition and/or leading to death.

Adverse events data collection**.**

Adverse events data will be collected from the start of the donor lymphocyte infusion to 30 days after that date or the last dose dose of AP1903 (which ever is later). Adverse event scoring will reflect the onset and resolution date and maximum grade; beyond this point some events considered related to chronic GvHD or late complications post transplant might be recorded only with the first date of their awareness with no grade or resolution date.

Microbiologically documented infections occurring within six months of initiation of DLI, including incidence of EBV-associated lymphoproliferative disorder or EBV reactivation; requiring therapy will also be recorded.

Intermittent events should be labeled as such and followed until resolution.

If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

As stated in the treatment plan, patients treated on this protocol will required supportive care treatment (concurrent medication). These medications are considered standard of care and have no scientific contributions to the protocol, therefore no data will be captured on the various medications needed or their sides effects.

AE and Protocol Deviations Reporting Requirements.

Adverse events will be reported accordingly to MDACC (HSRM chapter 15.001) and SCT&CT Department (HSRM chapter 15.053) policy and procedures.This study will be conducted in compliance however in the event of any protocol deviations or violations these will be reported accordingly to MDACC (HSRM chapter 25) and also according to IND sponsor - MDACC- IND Office requirements.

Serious Adverse Event Reporting (SAE)
for M. D. Anderson-Sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and the MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

- **The gene therapy reporting addendum ("Additional Reporting Form for Serious Adverse Events on Gene Transfer Trials") must be included with each SAE submitted.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12.0 Statistical Design

12.1 Study Design, monitoring and stopping criteria

This is a single-arm phase I/II trial of iCasp9-Modified T-cells given as a planned Donor Lymphocyte Infusion (DLI) following allogeneic hematopoietic stem cell therapy (alloHSCT) in subjects with a variety of hematologic malignancies (ALL, CML, CLL, Lymphoma, or Hodgkin's disease, multiple Myeloma or myelodysplastic syndrome). Patients must have either a matched related donor or matched unrelated donor willing to donate PBPC for post conditioning regimen stem cell support. There are up to three stages to this treatment regime. Stage 1, which includes all eligible patients, will consist of administration of the preparative regimen and alloHSCT followed by alemtuzumab and tacrolimus. These patients are at risk of transplant-related mortality within the first 100 days post transplant, TRM100. Approximately 10% of the patients in Stage 1 will experience early transplant related mortality or severe graft-versus-host disease, within the first 2 months. The remaining 90% of the alloHSCT patients in Stage 1 will be eligible for and receive iCasp9 modified DLI between 56 and 64 days post alloHSCT in Stage 2. These patients are at risk of unacceptable toxicity associated with the DLI within the first 28 days from the DLI, TOX28, defined as infusional related toxicity > Grade 3 for >24 hours or any grade 4 infusional toxicity occurring within 28 days of DLI administration. Of the patients who receive a DLI in Stage 2, approximately 50% will develop severe (grade 2 or above) GVHD, and will receive treatment with AP1903, which activates apoptosis of the iCasp9 modified cells with the goal of abrogating GVHD in Stage 3, with the goal to achieve a CR of GVHD within 14 days, CRG14. This is the primary efficacy outcome event of the trial. A maximum of 35 patients will receive alloHSCT. It is anticipated that 32 patients will receive a DLI, and 16 of these patients will develop severe GVHD and be treated with AP1903. The efficacy event CRG14 and the adverse events TOX28 and TRM100 will be monitored using the method of Thall, Simon, and Estey (1995).

STATISTICAL CONSIDERATIONS

1. Disease and Treatment Regime. This is a single-arm phase I/II trial of iCasp9-Modified T-cells given as a planned Donor Lymphocyte Infusion (DLI) following allogeneic hematopoietic stem cell therapy (alloHSCT) in subjects with a variety of hematologic malignancies (ALL, CML, CLL, Lymphoma, or Hodgkin's disease, multiple Myeloma or myelodysplastic syndrome). Patients must have either a matched related donor or matched unrelated donor willing to donate PBPC for post conditioning regimen stem cell support.

2. Stages of the Treatment Regime. There are up to three stages to this treatment regime:

Stage 1. Administration of the preparative regimen with alemtuzumab followed by HSCT and tacrolimus treatment. These patients are at risk of transplant-related mortality within the first 100 days post transplant, denoted by TRM100. Approximately 10% of the patients in Stage 1 will experience early TRM or severe graft-versus-host disease (GVHD), within the first 42 days.

Stage 2. The remaining 90% of the alloHSCT patients in Stage 1, who do not experience early TRM or severe GVHD, will be eligible for and receive iCasp9 modified DLI between days 56 and 64 post alloHSCT. These patients are at risk of unacceptable toxicity associated with the DLI within the first 28 days from the DLI, defined as infusional related toxicity > Grade 3 for >24 hours or any grade 4 infusional

toxicity occurring within 28 days of DLI administration. This adverse event is denoted by TOX28.

Stage 3. Of the patients who receive a DLI in Stage 2, it is anticipated that approximately 50% will develop severe (grade 2 or above) GVHD. These patients will receive treatment with AP1903, which activates apoptosis of the iCasp9 modified cells with the goal of abrogating GVHD. The goal of this stage of treatment is to achieve a complete remission of GVHD within 14 days, denoted by CRG14. This is the primary efficacy outcome event of the trial.

Given the above structure, the primary outcomes are the efficacy event CRG14, and the two adverse events TOX28 and TRM100.

3. Sample Sizes and Monitoring Rules. The maximum sample size is 35 patients enrolled to receive an alloHSCT. It is anticipated that .90x35 = 32 patients will receive a DLI, and that .90x.50x35 = 16 patients will receive a DLI and subsequently develop severe GVHD, thus requiring further treatment with AP1903. The following three monitoring rules will be implemented, two for safety and one for efficacy, using the Bayesian method of Thall, Simon, and Estey [1].

3.1 TRM100 in Stage 1: Let pTRM100 denote the probability of TRM100 in the 35 patients who receive an alloHSCT. Based on historical experience, it will be assumed that this probability follows a beta(.40,.60) prior, denoted pTRM100 ~ beta(.40, .60). The trial will be stopped due to excessive 100-day TRM if Pr(pTRM100 > .40 | data) > .95, with this rule applied after each successive cohort of 5 patients. (Patients who do not receive DLI will be replaced.) The resulting rule will stop the trial if [# patients with TRM100]/[number of patients evaluated] is greater than or equal to 4/5, 7/10, 10/15, 12/20, 15/25, or 17/30. The operating characteristics of this rule are as follows:

Table 1. Operating characteristics of the rule for monitoring 100-day TRM.

True Pr(TRM100)	Prob(Stop early)	Achieved Sample Size Quartiles
.40	.15	(35, 35, 35)
.55	.64	(5, 20, 35)
.60	.80	(5, 15, 30)

3.2 TOX28 in Stage 2: Let pTOX28 denote the probability of TOX28 in the patients who receive an alloHSCT and also subsequently receive a DLI. Based on historical experience, it will be assumed that pTOX28 ~ beta(.10, .90). The trial will be stopped due to excessive 28-day toxicity in Stage 2 if Pr(pTOX28 > .10 | data) > .90, with this rule applied after each successive cohort of 5 patients who receive DLI. The resulting rule will stop the trial if [# patients with TOX28]/[number of patients evaluated] is greater than or equal to 2/5, 3/10, 4/15, 5/20, 5/25, 6/30 or 7/35. The operating characteristics of this rule, assuming maximum sample size 32, are as follows:

Table 2. Operating characteristics of the rule for monitoring 28-day infusional-related toxicity in patients who receive a DLI.

True Pr(TOX28)	Prob(Stop early)	Achieved Sample Size Quartiles
.10	.18	(32, 32, 32)
.15	.44	(15, 32, 32)
.20	.69	(5, 20, 32)
.25	.86	(5, 10, 25)

3.3 CRG14 in Stage 3: Let pCRG14 denote the probability of achieving a CR of acute GVHD in the patients who receive an alloHSCT, subsequently receive a DLI, and subsequently develop acute GVHD. It will be assumed that pCRG14 ~ beta(.50, .50). The trial will be stopped due to an unpromising low 14-day CR of aGVHD rate in the 16 patients treated in Stage 3 if Pr(pCRG14 > .50 | data) < .05, with this rule applied after each successive cohort of 4 patients. The resulting rule will stop the trial if [# patients

with CRG14]/[number of patients evaluated] is less than or equal to 0/4, 1/8, 3/12, 4/16, 6/20 or 7/24, where boundaries beyond the anticipated 16 patients have been included in case the achieved subsample size is larger than 16. The operating characteristics of this rule, assuming maximum sample size 16, are as follows:

Table 3. Operating characteristics of the rule for monitoring 28-day infusional-related toxicity in patients who receive a DLI.

True Pr(CRG14)	Prob(Stop early)	Achieved Sample Size Quartiles
.20	.82	(4, 8, 12)
.30	.55	(8, 12, 16)
.40	.28	(12, 16, 16)
.50	.11	(16, 16, 16)

4. Secondary Outcomes. Secondary outcomes will include overall survival (OS) time.

5. Data Analysis. The data will be analyzed by tabulating the primary events and computing Bayesian credible intervals for their probabilities. OS will be estimated by the method of Kaplan and Meier [2].

6. References

[1] Thall PF, Simon R, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat in Medicine 14:357-379, 1995.

[2] Kaplan, EL and Meier, P: Nonparametric estimator from incomplete observations. J. American Statistical Association 53:457-481, 1958.

12.1.2 Demographic and Baseline Characteristics
Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, risk status, acute GvHD grade at enrollment, donor type and HLA matching, donor age, donor gender, and donor ethnicity. Between group comparisons will be performed for continuous variables via a t-test and for categorical variables, via the chi-square test.

12.1.3 Analysis of Primary Endpoint
Probabilities of persistent GVHD free survival will be estimated using Kaplan-Meier estimators, with the primary analysis population defined as those patients who receive DLI, and an event defined as either death or development of acute GVHD which persists for at least 14 days or which requires steroid therapy for more than 14 days. The mean restricted time alive without persistent acute GVHD will be calculated up to day 180 for each group, and the groups will be compared using a two-sample Z statistic based on the difference in restricted means.

12.1.4 Analysis of Secondary Endpoints

12.1.4.1 The Time to complete resolution of aGvHD which is durable for at least 14 days after administration of AP1903 in subjects that develop GvHD after DLI
Probability of resolution of aGVHD over time will be described in each treatment group using the cumulative incidence estimator, treating death without resolution as a competing risk. These curves will be compared between the two groups using Gray's test.

12.1.4.2 Disease-Free Survival at 6 months and post DLI
Disease-free survival will be estimated using the Kaplan-Meier estimate at 6 months post enrollment and at 6 months post DLI. The median DFS and its 95% confidence interval will also be described if reached. The disease free survival curves will be compared between the two treatment groups using the log-rank

test.

12.1.4.3 Non-Relapse Mortality at 6 months and post DLI
Non-relapse mortality will be estimated using the cumulative incidence method, treating relapse as the competing risk. The cumulative incidence curves for non-relapse mortality will be compared between the treatments using Gray's test.

12.1.4.4 Disease relapse at 6 months and post DLI
Disease relapse will be estimated using the cumulative incidence method, treating death as the competing risk. The cumulative incidence curves for disease relapse will be compared between the treatments using Gray's test.

12.1.4.5 Overall and GvHD-free Survival at 6 months and post DLI
Overall survival and GvHD-free survival will be estimated using the Kaplan-Meier estimate at 6 months post enrollment and at 6 months post DLI. For GvHD-free survival an event will be death or development of GvHD. The median survival and median GVHD-free survival will also be described along with the respective 95% confidence intervals if reached. The overall survival and GvHD free survival curves will be compared between the two treatment groups using the log-rank test.

12.1.4.6 Incidence of Systemic Infections within 6 months
Frequencies of infections will be tabulated by site of disease, date of onset, and severity. The time to first serious infection will be described using the cumulative incidence function with death as the competing risk, and compared between treatments using Gray's test.

12.1.4.7 Proportion of subjects requiring a ≥7 day hospitalization post DLI and post administration of AP1903
The proportion of subjects requiring a ·7 day hospitalization will be described using frequencies and compared between treatment groups using the Fishers exact test.

12.1.4.8 Incidence of EBV-associated lymphoproliferative disorder or EBV reactivation requiring therapy and post DLI
The incidence of EBV-associated lymphoproliferative disorder or EBV reactivation therapy post enrollment and post DLI will be described using the cumulative incidence function, treating death as the competing risk. Cumulative incidence curves will be compared between treatments using Gray's test.

12.1.4.9 Proportion of patients developing Gr I-IV acute GvHD and chronic GvHD by Day 28, 56 and 180 post DLI.
The incidence of acute and chronic GvHD will be computed using the cumulative incidence estimator, treating death prior to acute or chronic GvHD as a competing risk. Pointwise confidence intervals will be provided at Day 28, 56, and 180 post-DLI. The cumulative incidence curves will be compared using Gray's test.

12.1.4.10 Treatment failure (treatment failure defined as: no response, progression, administration of additional therapy for GvHD, or mortality) among surviving subjects at Day 3, 7, 14, 28, and 56 post administration of AP1903.
The proportion of subjects with treatment failure among surviving subjects at Days 3, 7, 14, 28, and 56 will be compared between the two treatment groups using the Fishers exact test.

12.1.4.11 The incidence of acute GvHD flare after CR/PR requiring additional agent (including 2.5 mg/kg/day of prednisone [or methylprednisolone equivalent of 2 mg/kg/day]) for systemic therapy before Day 56 post-administration of AP1903.
The proportion of subjects experiencing an acute GvHD flare after CR/PR requiring additional agent of prednisone will be evaluated at Day 56 post-administration of AP1903

12.1.4.12 Incidence of discontinuation of immune suppression without acute GvHD flare and

without disease progression/recurrence by Days 3, 7, 14, 28, 56, and 180 post-administration of AP1903.
The proportion of subjects discontinuing immune suppression without acute GvHD flare and without disease progression/recurrence by Days 3, 7, 14, 28, 56, and 180 post-administration of AP1903 will be compared using the Fishers exact test at each time point.

12.1.4.13 Steroid dose at Day 3, 7, 14, 28 and 56 post-administration of AP1903.
The median and range of steroid doses at each time point will be provided separately for each treatment group. The median steroid dose will be compared using the Wilcoxon rank sum test.

12.1.4.14 Incidence of topical/non-absorbable therapy given by Day 56 post-administration of AP1903.
The proportion of subjects using topical/non-absorbable therapy by Day 56 will be compared using the Fishers exact test.

12.1.4.15 Change in patient-reported outcomes.
Participant self-reported measures will be assessed using the MDASI at enrollment, at the time of DLI, at the occurence of GVHD before receiving AP1903, and approximately 7 and 14 days after receiving AP1903. Patients who do not develop GVHD post DLI will complete the questionnaire approximately one month later.

The MDASI will be scored according to the recommendations of the developers. We will explore the range of scores to assess the medians, means and standard deviations observed. Using repeated measures longitudinal models, we will use PROC MIXED to explore changes over time and major domains that differ between patients on the two trial arms. In exploratory analyses, we will also investigate the clinical relevance of particular items in the MDASI, including the items which correlate with different organ manifestations of acute GvHD and the items most sensitive to change when acute GvHD improves objectively.

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