Title: Parallel Phase II Trial of Adoptive Immunotherapy Targeted Against Inherited Paternal Antigens (IPA) vs Adult Haplo-Identical Cell Infusion During Induction of High Risk Leukemia or Myelodysplastic Syndrome

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Weill Cornell Medical College

TITLE: Parallel phase II trial of adoptive immunotherapy targeted against Inherited Paternal Antigens (IPA) vs adult haplo-identical cell infusion during induction of high risk leukemia or myelodysplastic syndrome; Version Date: July 15, 2022

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SCHEMA

STUDY SCHEMA

1. **INCLUSION/EXCLUSION: See Section 3**

ENROLLMENT: All potential recipients will have complete HLA typing (12 loci). An appropriate umbilical cord blood unit (CBU) will be identified or in the absence of an appropriate CBU, a haplo-identical donor will be identified.

INDUCTION THERAPY:
Will be at treating physician's choice, and could include cytarabine-daunorubicin (3+7). High dose cytarabine-mitoxantrone or other appropriate regimens. For patients with MDS or AML patients considered unfit for intensive therapy, it can include treatment with hypomethylating agents.

STEM CELL ADMINISTRATION
Within 72 hours after completion of the chemotherapy regimen, and no sooner than 24 hours after administration of the last dose of chemotherapy, umbilical cord graft or haplo-graft will be administered.
Supportive care and premedications for stem cell administration will be governed by current policies of transplant program.

The choice between CBU vs Haplo-graft will be based on availability according to the table below. It may be further influenced by practical issues such as insurance approval etc.

Graft selection algorithm		
1	**CBU Unit 5/6 Matched**	**1 NIMA match with patient**
2	**CBU Unit 5/6 Matched**	**Shared IPA target(s) with patient**
3	**Haplo Identical relative**	
4	**CBU Unit 4/6 matched**	**1-2 NIMA matches with patient**
5	**CBU Unit 4/6 matched**	**Shared IPA target(s) with patient**

CBU UNIT The CBU unit must supply a minimum of 0.5 $x10^7$/kg and a maximum of 2.5$x10^7$/kg nucleated cell dose pre-cryopreservation. The unit must match at a minimum of 4 of 6 at HLA-A, -B antigens, -DRB1 alleles with the recipient. Mismatches (0-2) can be at any loci -. Although molecular level typing will be available for the patient and the CBU unit, a match is defined at intermediate resolution for HLA-A and –B and at high resolution for –DRB1. The CBU donor will also have undergone HLA typing of the mother, thus allowing determination of the CBU-IPA and NIMA.
CBU grafts used in this study will be investigational units that meet all criteria for clinical use.
Better matching units will be preferred over less matching units as long as the CBU dose exceeds 0.5 $x10^7$ NBC/kg

ALL RECIPIENTS SHOULD HAVE TESTING FOR CLASS I AND CLASS II HLA ANTIBODIES. IF ANTIBODIES ARE PRESENT, CBU SHOULD BE CHOSEN THAT ARE NOT TARGETED. THIS MAY REQUIRE DQ AND DP TESTING OF THE CBU.

HAPLO UNIT
Haplo identical healthy related donor. Ie. Parent, child, sibling, possibly third degree or farther removed relative (cousin, aunt, nephew etc…).
They will be collected using standard methods and approximately 3 x10^6 CD34 cells/kg will be infused within 72 hours after completion of the treatment.

Note: Excess cells collected from the haplo-identical donor will be cryopreserved and may be reinfused if deemed clinically necessary during subsequent off protocol treatments.

Supportive Care and Management of Side Effects:

Supportive care will follow the institutional standards of care for treatment of leukemia patients. (e.g. quinolone prophylaxis, antifungal prophylaxis, antiviral prophylaxis).
In addition patients will be monitored weekly for CMV reactivation. CMV viremia will be treated appropriately.

No GVHD prophylaxis will be administered, but patients will be closely monitored for signs and symptoms of GVHD. Suspicion for GVHD will be confirmed by biopsy. GVHD grade II and above will preferably be treated with a single dose of cyclophosphamide 50 mg/kg with mesna.

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1. OBJECTIVES

1.1 Primary Objective

To evaluate the safety of adoptive immunotherapy with Non-Inherited Maternal Antigen (NIMA) compatible, Inherited Paternal Antigen (IPA) targeted CBU or with haplo-identical stem cells after conventional induction therapy for very high risk Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS).

1.2 Secondary Objectives

a) To assess the incidence and severity of Graft Versus Host Disease (GVHD), after conventional induction therapy followed by adoptive immunotherapy with NIMA compatible, IPA targeted CBU.

b) To assess the incidence and severity of GVHD, after conventional induction therapy followed by adoptive immunotherapy with haplo-identical stem cells.

c) To study kinetics of graft chimerism (including UCBM-microchimerism) after each of these treatments

d) To study development of HLA-antibodies after each of these treatments

e) To assess response rates and duration of response after each of these treatments

f) To assess the utilization of unrelated, low cell dose CBU as adoptive immunotherapy for AML

2. BACKGROUND

2.1 Acute Leukemia and MDS

Acute leukemia and MDS used to be invariably fatal diseases, but over the past decades, outcomes have much improved.[1-3] Younger patients and those with favorable features can often be cured; for older patients and those with unfavorable features induction of remission and prolongation of life has become a realistic goal of treatment. But survival and quality of life tend to correlate with induction of response. Approximately 60% of patients obtain first remission after initial treatment and have a reasonable prognosis. Those failing to obtain a first remission have a poor prognosis. Well defined unfavorable characteristics include older age, monosomal karyotype and complex karyotype.[4;5]Patients who have achieved an initial CR to conventional therapy and relapse within less than a year from diagnosis, also have less than 20% chance of obtaining a second remission.

Over the past decade hypomethylating agents (azacytidine and deoxyazacytidine) have been shown to induce remissions and prolong survival in older patients with AML and MDS. But remissions are not durable and upon disease progression, outcomes are poor.

Remission rates upon reinduction with conventional chemotherapy are low and median overall survival is in the range of three to four months.

Outcome of patients with AML and/or MDS who fail hypomethylating agents			
Author	Nr of pts	Median Survival	CR/CRp
Prebet (MDS)[6]	435	5.6 months	14%
Prebet(AML)[7]	74	3 months	none
Bello[8]	25	3.7 months	30%
Jabbour[9]	87	4.3 months	20%
Ritchie[10]	81*	5 mo**	
*patients who failed induction with hypomethylating agents.** from start of hypomethylating agent.			

In a somewhat similar analysis, the MD Anderson Cancer Center group has analyzed the outcome of patients with AML undergoing second salvage therapy, and identified prognostic factors associated with remission and survival in a cohort of 594 patients. Salvage therapy included Allogeneic Stem Cell Transplantation (SCT) in 74 patients, standard-dose ara-C combinations in 30 patients, high-dose ara-C combinations in 171 patients, non-ara-C combinations in 73 patients, and phase I-II single agents in 246 patients. Overall, 76 patients (13 %) achieved Complete Remission (CR). The median CR duration was 7 months. The median survival was 1.5 months, and the 1-year survival rate was 8 %. A multivariate analysis of prognostic factors for CR identified the following 6 independent adverse factors: (1)CR1 duration < 6 months; (2)CR2 duration < 6 months; (3) salvage therapy not including allogeneic SCT; (4)non-inversion 16 AML; (5) platelet counts < 50 x 10^9/L, and (6) leukocytosis > 50 x 10^9/L. Patients were divided into low-risk (1-2 adverse factors; 8 %), intermediate 1 (3 factors; 20 %), intermediate 2 (4 factors; 38 %), and high-risk groups (5-6 factors; 33 %) with respective CR rates of 54 %, 26 %, 8 %, and 0 %. The respective 1-year survival rates were 36 %, 21 %, 6 %, and 1 %. A multivariate analysis for survival identified the following 6 independent adverse factors: (1) CR1 duration < 12 months; (2) CR2 duration < 6 months; (3) bilirubin level ≥ 1 mg/dL; (3) albumin level < 3 g/dL; (4) age > 60 years; (5) bone marrow blasts ≥ 50 %; and (6) year of therapy before 1991. Patients were divided into low-risk (0-2 adverse factors; 39 %), intermediate (3 factors; 27%), and high-risk groups (≥ 4 factors; 34 %) with estimated 1-year survival rates of 22 %, 6 %, and 0 %, respectively.

The proposed study will focus on this subgroup of patients who have limited treatment options.

2.2 Adoptive immunotherapy in AML

Cellular therapy, particularly as used in allogeneic transplantation, is an established treatment for AML.[11] So-called Graft-Versus-Leukemia (GVL) effects can be powerful mediators of anti-leukemic therapy. Unfortunately, because of its associated toxicities and the difficulties in finding matching donors, allogeneic transplant is applicable to only a minority of patients. Typically, it is offered to those with an excellent performance status, who have compatible donors and who have achieved at least some disease control, preferably CR. Those who fail to achieve a complete remission are not often considered for transplant, and if they are, their outcome is far inferior.[12]

Several groups have recently reported on the value of adoptive cellular therapy during induction. In those circumstances, the graft is thought to mediate transient GVL effects and then be rejected. Colvin et al, reported a pilot study of haploidentical cell infusion in a Phase I/II nonimmunosuppressive, nonmyeloablative setting.[13] A total of 41 patients with relapsed refractory cancer received 100 cGy of total body irradiation (TBI), along with an infusion of haplo-identical cells. There were 26 patients with hematologic malignancies with 14 responses, 9 of which were major; there were 5 durable complete responses and 4 partial responses in 13 patients with acute myelogenous leukemia (AML). All responses occurred without overt donor chimerism.

Guo et al reported fifty-eight AML patients aged 60-88 years who were randomly assigned to receive induction chemotherapy with cytarabine and mitoxantrone or the same chemotherapy plus G-CSF mobilized HLA-haplo-identical stem cells(G-PBSC).[14] Patients who achieved complete remission received another 2 cycles of post remission therapy with intermediate-dose cytarabine or the same chemotherapy plus G-PBSCs. The complete remission rate was significantly higher in the G-PBSC group than in the control group (80.0% vs 42.8%; $P < .006$). The median recovery times of neutrophils and platelets were 11 days and 14.5 days, respectively in the G-PBSC group and 16 days and 20 days, respectively, in the control group after chemotherapy. The 2-year probability of disease-free survival was significantly higher in the G-PBSC group than in the control group (38.9% vs 10.0%; $P < .01$). No graft-versus-host disease was observed in any patient. Persistent donor microchimerism was successfully detected in the 4 female patients who received cells from male donors.

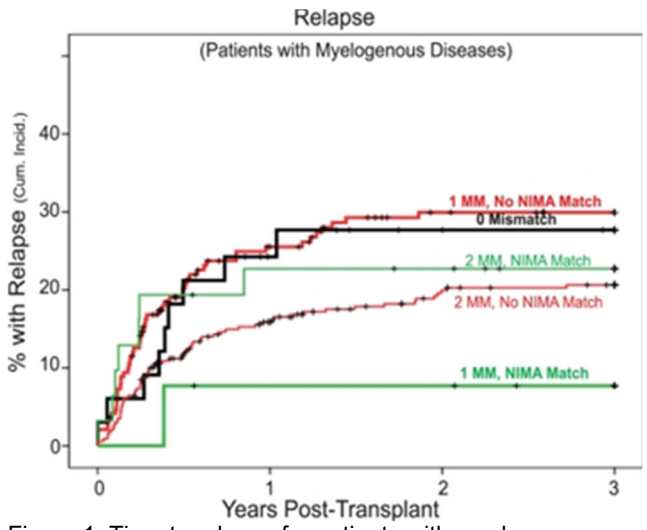

Figure 1: Time to relapse for patients with myelogenous malignancies. Zero HLA mismatch (MM) = 33; one MM/NIMA match = 13; two MM/NIMA match = 31; one MM/no-NIMA match = 193; two MM/no-NIMA match = 343.

The studies from these groups, though preliminary studies, suggest that GVL effects can contribute to induction of remission and that they may be operative with minimal or transient evidence of chimerism. Indeed, transient or mixed chimerism may be preferable because it is associated with less risk for acute or chronic GVHD.[15;16]

2.3 Umbilical Cord Blood Transplant and GVL Effect

Several groups, including our own, have shown decreased rates of disease recurrence after umbilical cord blood transplantation compared to unrelated donor transplant.[17] (and Delaney, personal communication). The reasons for the reduced rate of disease recurrence after CBU transplant have until recently remained elusive, but may be explained by the presence in the umbilical cord graft of a substantial number of lymphocytes of maternal origin that are primed against the paternal HLA-haplotype of the fetus (the inherited paternal antigen or IPA). The first indication of this mechanism came from the observation by Mold et al that fetal lymphoid organs including the lymph nodes and blood contain between 0.1% and 0.5% lymphocytes of maternal origin.[18] These lymphocytes are protected from immune-mediated destruction by the presence of a very high number of fetal T-regulatory cells. Van Rood et al speculated that the IPA-primed maternal cells were responsible for the GVL activity of the cord and that a similar mechanism explained why haplo-identical transplant from a mother to her child is associated with less relapse than that from a father. In an elegant study, they analyzed for a large number of CBU transplants, the HLA type of both mother and CBU and deduced the IPA of the CBU.[19] Then, they identified transplant cases with IPA targeting CBU (i.e cases in which the maternal lymphocytes would be primed against the IPA of the CBU and also against the recipient.) They compared their outcome with that of the cases where there was no IPA reactivity and found a much increased rate of disease recurrence in the latter. This phenomenon was mostly observed in recipients of well-matched transplants (5/6 matched). Importantly, the decreased recurrence rate after IPA targeted CBU-SCT was not associated with increased GVHD.

Another set of HLA molecules, the NIMA (non-inherited maternal antigens, i.e antigens absent from the CBU cells, but present in the mother of the fetus), also merit consideration. The CBU cells have been exposed to these NIMAs throughout their life span (throughout pregnancy), and therefore are tolerant to them. In the setting of CBU stem cell transplant, the presence of NIMA in the transplant recipient results in

improved transplant outcomes even when grafts with low TNC doses were used.[19] (Figure 1)

2.4 Rationale for the Current Study: Potential Benefits

Preliminary data indicates that adoptive cellular therapy with partially matched cells is an effective approach that may improve remission rates and survival in AML and MDS. Rates of remission and survival for patients with AML and MDS who fail hypomethylating agents are extremely poor. We have focused on this well-defined subgroup for our initial studies.

The majority of preliminary data on adoptive immunotherapy derives from infusion of haplo-identical cells after induction therapy. Organization of haplo-identical cell therapy during remission induction of acute leukemia may pose considerable logistical problems in the United States. For example, only a small minority of older patients have siblings that can be readily tested. [20] Children, who could serve as haplo-identical donors, are often not readily available for a variety of reasons, such as remote distances, socio-economic issues, health etc. An increasing number of people- up to 20%- also remain childless - a percentage that is likely to increase given recent demographic trends.[21] Logistical, financial and availability issues thus limit the practicality of this type of intervention. Lastly, recent data suggest that genomic loss of is an extremely common mechanism of escape of tumor surveillance from the GVL effects mediated by partially mismatched grafts.[22]

As an alternative, we are interested in exploring the utility of umbilical cord blood infusion as a means of inducing antileukemic effects. Umbilical cord blood cells are banked and readily available and because of IPA-mediated effects have potent antileukemic effects and cause less GVHD, and may therefore be superior at inducing remissions compared to haplo-identical grafts. These IPA-mediated GVL effects were mostly detected in recipients of 5/6 matched grafts. Low resolution and partial HLA-matching is sufficient for identification of an appropriate umbilical cord blood unit. Since

The likelihood of finding CBU grafts of different cellular content and degree of matching for various ethnic groups are shown in Table 1 (M Maiers, personal communication). 5/6 HLA matched cords can be found in up to 75% of patients of most ethnic groups, if smaller than customary cell doses are accepted; 4/6 matched CBU can be identified for nearly all patients.

Table 1: Likelihood of identifying an CBU graft for various ethnic groups, based on current inventory size and cell does requirement.

	HLA 5/6 matched graft			HLA 4/6 matched graft		
	TNC2.5	TNC1.5	TNC0.5	TNC2.5	TNC1.5	TNC0.5
AAFA	0.20	0.51	0.74	0.77	0.98	1.00
AFB	0.19	0.51	0.73	0.76	0.98	1.00

CARB	0.20	0.52	0.74	0.76	0.98	1.00
SCAMB	0.23	0.54	0.74	0.78	0.98	1.00
AINDI	0.35	0.70	0.86	0.86	0.99	1.00
FILII	0.32	0.72	0.89	0.83	0.99	1.00
HAWI	0.25	0.57	0.76	0.78	0.97	1.00
JAPI	0.29	0.68	0.87	0.83	0.99	1.00
KORI	0.32	0.70	0.88	0.85	0.99	1.00
NCHI	0.33	0.72	0.89	0.85	0.99	1.00
SCSEAI	0.30	0.65	0.83	0.85	0.99	1.00
VIET	0.32	0.69	0.86	0.83	0.99	1.00
MENAFC	0.42	0.74	0.88	0.89	0.99	1.00
EURCAU	0.63	0.89	0.96	0.95	1.00	1.00
CARHIS	0.36	0.70	0.86	0.87	0.99	1.00
MSWHIS	0.40	0.75	0.89	0.89	0.99	1.00
SCAHIS	0.40	0.74	0.88	0.89	0.99	1.00
AISC	0.50	0.79	0.90	0.91	0.99	1.00
ALANAM	0.42	0.73	0.88	0.89	0.99	1.00
AMIND	0.50	0.80	0.92	0.92	1.00	1.00
CARIBI	0.30	0.62	0.81	0.83	0.99	1.00

Population	Broad race	Description
AAFA	**AFA (African American)**	African American
AFB		African
CARB		Black Caribbean
SCAMB		Black South or Central American
AINDI	**API (Asian or Pacific Islander)**	South Asian
FILII		Filipino
HAWI		Hawaiian/other Pacific Islander
JAPI		Japanese
KORI		Korean
NCHI		Chinese
SCSEAI		Other Southeast Asian
VIET		Vietnamese
MENAFC	**CAU (Caucasian)**	Mideast/North Coast of Africa
EURCAU		European Caucasian
CARHIS	**HIS (Hispanic)**	Caribbean Hispanic
MSWHIS		Mexican or Chicano
SCAHIS		South or Central Amer. Hispanic
AISC	**NAM (Native American)**	Amer. Indian South or Central America
ALANAM		Alaska Native or Aleut
AMIND		North American Indian
CARIBI		Caribbean Indian

In this initial study, we propose to utilize either haplo-identical cells or CBU cells depending on availability and our selection criteria. This will allow us to compare in a preliminary fashion the toxic (GVHD, myelosuppression, development of HLA antibodies to the donor) and therapeutic effects (count recovery, response rate) of each of these products.

The biological effects of the CBU infusions is immunologically and largely T-cell mediated. Moderate doses of T-cells as low as 0.2-1x10^6 CD3/$kg_{(recipient)}$ have been associated with beneficial effects in the adoptive therapy of viral diseases and likely also mediate GVL effects.[23] Approximately 30 % of the cellular content of a CBU unit consists of Tcells. CBU with a cell dose as low as 5x10^6/kg_r nucleated cells will be permissible. The highest acceptable nucleated cell dose will be 25x10^6/kg_r

2.5 Rationale for the Current Study: Potential Risks

The risks of adoptive cell therapy include the development of graft vs host disease, prolongation of myelosuppression and development of donor specific antibodies that may interfere with further therapy. A syndrome akin to engraftment syndrome, but seemingly mediated by other cytokines and labeded "haplo-immunostorm" has also been described.[13] Based on preliminary experience by others, we believe that such risks are extremely low.[14] Nevertheless, a major goal of the proposed studies is to detect toxicities and stopping rules are incorporated in case of excessive toxicity.

2.6 Preliminary Results November 2017

As of July 2017, ten patients have been treated with the CBU graft (Table); 8 had AML, 7 with primary induction failure (PIF); one had myeloid blast phase CML and one with high risk MDS. Nine patients had poor risk karyotype and 4 had prior allografts. Median age was 52 years (range: 34-67); median number of prior treatments was 11 (2-15) and median HSCT-CI was 3 (0-7).

No CBU infusion reactions or cytokine release syndrome were observed. One patient, recipient of a prior allograft with no history of GVHD, experienced skin rash 1 week after CBU infusion. The skin biopsy was consistent with GVHD. No GVHD was observed in the other 9 patients. One patient died of disseminated adenovirus infection early after treatment, viremia was present at the initiation of chemotherapy.

Transient CBU chimerism was detected in 5 of the 10 patients as early as one week and as late as 6 months after CBU infusion. The median bone marrow blast percentage before treatment was 27% (range: 10-98) and at one month +/- 7 days post treatment was 8% (range: 0-90). Five patients had objective hematologic responses, 4 with aplasia and one with a partial response, while 5 patients recovered with persistent leukemia. Six patients went on to receive hematopoietic stem cell transplants (HSCT). Two subsequently relapsed and one died of disseminated adenovirus, while 3 patients remain in remission. These three patients also remain in remission as of November 09, 2017. These data will be presented at the ASH meeting in 2017, Three additional patients have been treated since then, though follow-up is short, two additional

remissions have been observed in very heavily pretreated patients. One of the latter patients developed grade IV GVHD which has been reversed.

3. PATIENT SELECTION

3.1 Inclusion Criteria (Modified 5/26/2020)

Patients can be of any race and either gender and must meet all of the following criteria to be eligible for participation in this study.

1. Patients must be 18 years of age or older
2. Patients with a confirmed diagnosis of AML or MDS, according to WHO classification (excluding acute promyelocytic leukaemia) with recurrent or refractory disease as defined below.
    a. For AML:
        (1) Primary induction failure (PIF) after ≥ 2 cycles of chemotherapy.
        (2) First relapse -only if occurring within 12 months from initial induction therapy.
        (3) Relapse refractory to salvage chemotherapy
        (4) Second or subsequent relapse.

        Patients who fail targeted agents including IDH1, IDH2 or FLT3 inhibitors will be eligible if they fulfill other eligibility criteria.
        Patients who fail venetoclax based therapy will be eligible if they fulfill other eligibility criteria.

    b. For MDS, either RAEB I or RAEB II who failed at least one chemotherapy regimen including either cytarabine or a hypomethylating agent.
        Failure of cytarabine or hypomethylating agent will include patients who fail to achieve PR after four cycles of treatment.

Addendum 5/26/2020
Patients who fail targeted agents including IDH1, IDH2 or FLT3 inhibitors will be eligible if they fulfill other eligibility criteria.
Patients who fail venetoclax based therapy will be eligible if they fulfill other eligibility criteria.

3. Patients must have Karnofsky Performance score of ≥70
4. Women of child-bearing potential must have a negative serum or urine pregnancy test within 2 weeks prior to treatment start
5. Patients must be capable of understanding and complying with protocol requirements, and must be able and willing to sign a written informed consent form

3.2 Exclusion Criteria

Patients who meet any one of the following criteria will not be eligible for study participation

1. Persistent clinically significant toxicities from previous chemotherapy
2. Known positive status for human immunodeficiency virus (HIV)
3. Pregnant and nursing patients
4. Uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, or psychiatric illness/social situations that would limit compliance with study requirements
5. Impairment of hepatic or renal function to such an extent that the patient, in the opinion of the investigator, will be exposed to an excessive risk if entered into this clinical study
6. Active heart disease including myocardial infarction within previous 3 months, symptomatic coronary artery disease, arrhythmias not controlled by medication, or uncontrolled congestive heart failure. Any NYHA grade 3 or 4.
7. Any medical condition which in the opinion of the investigator places the patient at an unacceptably high risk for toxicities

Note: AML and MDS are life-threatening diseases and participation in this protocol may at times constitute the treatment option most likely to benefit a particular patient. Therefore, the exclusion criteria may be waived if - in the opinion of the referring leukemia specialist and the transplant team - this constitutes the best therapeutic option.

4.0 ENROLLMENT AND REGISTRATION PROCEDURES

4.1 Enrollment

All potential recipients will have complete HLA typing and determination of HLA antibodies. An appropriate umbilical cord blood unit (CBU) will be identified or in the absence of an appropriate CBU, a haplo-identical donor will be identified.

4.2 Central Patient Registration

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5. TREATMENT PLAN

5.1 Induction therapy

Will be at treating physician's choice and could include cytarabine-daunorubicin (3+7). High dose cytarabine-mitoxantrone or other appropriate regimens.[5;24] For patients with MDS or AML patients considered unfit for intensive therapy, it can include treatment with hypomethylating agents.

5.2 Stem Cell Source and Cell Dose

Within 72 hours after completion of the chemotherapy regimen, and no sooner than 24 hours after administration of the last dose of chemotherapy, umbilical cord graft or haplo-graft will be administered.

Supportive care and premedications for stem cell administration will be governed by current policies of transplant program.

The choice between CBU vs Haplo-graft will be based on availability according to the table below. It may be further influenced by practical issues such as insurance approval etc.

Graft selection algorithm		
1	**CBU Unit 5/6 Matched**	**1 NIMA match with patient**
2	**CBU Unit 5/6 Matched**	**Shared IPA target(s) with patient**
3	**Haplo Identical relative**	
4	**CBU Unit 4/6 matched**	**1-2 NIMA matches with patient**
5	**CBU Unit 4/6 matched**	**Shared IPA target(s) with patient**

5.3 CBU UNIT The CBU unit must supply a minimum of 0.5 $x10^7$/kg and a maximum of 2.5$x10^7$/kg nucleated cell dose pre-cryopreservation. The unit must match at a minimum of 4 of 6 at HLA-A, -B antigens, -DRB1 alleles with the recipient. Mismatches (0-2) can be at any loci -. Although molecular level typing will be available for the patient and the CBU unit, a match is defined at intermediate resolution for HLA-A and –B and at high resolution for –DRB1. The CBU donor will also have undergone HLA typing of the mother, thus allowing determination of the CBU-IPA and NIMA.

CBU grafts used in this study will be investigational units that meet all criteria for clinical use. Better matching units will be preferred over less matching units as long as the CBU dose exceeds 0.5 $x10^7$ NBC/kg

ALL RECIPIENTS SHOULD HAVE TESTING FOR CLASS I AND CLASS II HLA ANTIBODIES. IF ANTIBODIES ARE PRESENT, CBU SHOULD BE CHOSEN THAT ARE NOT TARGETED. THIS MAY REQUIRE DQ AND DP TESTING OF THE CBU.[25-27]

5.4 HAPLO UNIT

Haplo-identical healthy related donor. i.e. Parent, child, sibling, possibly third degree or further removed relative (cousin, aunt, nephew etc)

They will be collected using standard methods and approximately 3 x10^6 CD34 cells/kg will be infused within 72 hours after completion of the treatment.

Note: Excess cells collected from the haplo-identical donor will be cryopreserved and may be reinfused if deemed clinically necessary during subsequent off protocol treatments.

5.5 Supportive Care and Management of Side Effects including Engraftment, GVHD and Haplo-Immunostorm. Modified 5/26/2020

Supportive care will follow the institutional standards of care for treatment of leukemia patients. (e.g. quinolone prophylaxis, antifungal prophylaxis, antiviral prophylaxis).
In addition patients will be monitored weekly for CMV reactivation. CMV viremia will be treated appropriately.

Modified 5/26/2020
No GVHD prophylaxis will be administered, but patients will be closely monitored for signs and symptoms of GVHD. Suspicion for GVHD will be confirmed by biopsy. GVHD grade II and above will preferably be treated with a single dose of cyclophosphamide 50 mg/kg. Subsequent treatment, if required, will follow standard transplant SOP and will include high dose steroids (0.5 mg/kg-2 mg/kg depending on severity). Administration of high dose cyclophosphamide may not always be feasible and in such cases, steroids will be the first line of therapy.

GVHD Prophylaxis and Treatment. Added 5/26/20
Complete and durable donor chimerism has been observed in minority of patients. This has been associated with a high incidence of grade 3 and 4 acute GVHD.
The observation of >50% donor chimerism at any time after graft infusion will lead to institution of GVHD prophylaxis preferably with **calcineurin inhibitors**. Alternatives include **mTor inhibitors, steroids and/or mycophenolate.**

Haplo-immunostorm Modified 5.26.20.
Haplo-immunostorm defined by fever, rash, diarrhea and liver function abnormalities without histological evidence for GVHD is a syndrome very similar to cytokine release syndrome.
It will be graded and managed in a similar fashion. (Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-38.) and Table below

Grading of Cytokine Release Syndrome (CRS) (ASBMT CRS Consensus Grading)[13]

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	≥ 38°	≥ 38°	≥ 38°	≥ 38°
Hypotension	None	Not requiring vasopressors†	Requiring vasopressors with or without vasopressin	Requiring multiple vasopressors (exluding vasopressin)
And/or Hypoxia**	None	Requring low-flow nasal cannula*** or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature >= 38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

** CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

*** Low-flow nasal cannula is defined as oxygen delivered at 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

†Vasopressin is not included in the assignment of CRS grade

Grade 5 CRS: By convention, grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome

CRS Management by Grade

Grade	Management
Grade 1	• Provide symptomatic support: - Administer antipyretics around the clock, if necessary - Administer oxygen, pain meds, intravenous fluids as needed - Empiric broad spectrum antibiotics if neutropenic • Consider tocilizumab for persistent (> 3 days) or refractory fever
Grade 2	• Provide symptomatic support as in Grade 1 • Consult ICU Triage • Start continuous cardiac telemetry and continuous pulse oximetry • Start supplemental oxygen • If hypotensive, give fluid bolus of 500-1000 mL

Grade 3	• Continue Grade 1 and 2 measures • Manage hypoxia and hypotension with supportive care measures as needed • If hypotensive after 2 boluses, start vasopressors and consider transfer to ICU • Consider tocilizumab; repeat up to every 8 hours if not responsive to intravenous fluids or supplemental O2. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses • If hypotension persists after 1-2 doses of tocilizumab or there are signs of hypo-perfusion or rapid deterioration, start dexamethasone 10mg Q6hr[2] • Consider G-CSF if neutropenic[3]
Grade 4	• Administer tocilizumab if not done earlier • Start methylprednisolone 1000 mg IV Q24H[2]

6.0 RECIPIENT PRE-TREATMENT EVALUATION

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1. Medical history, physical examination, vital signs, height and weight.
2. Karnofsky Performance Status.
3. CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, ALT, and AST.
4. CMV antibody test, hepatitis panel (HepA Ab, HepB Sab, HepB Sag, HepB Core Ab, HepCAb), herpes simplex, syphilis, HIV and HTLV 1 antibody, and varicella zoster virus.
5. High resolution HLA typing, if not already performed.
6. Bone marrow aspirates for pathology and cytogenetics and/or biopsy, for patients with <10% circulating peripheral blasts.
7. CMV PCR, EBV PCR
8. HLA antibodies
9. Assessment of disease status (bone marrow, cytogenetics, molecular testing etc..) within 30 days prior to start of chemotherapy.
10. CRP, ESR (erythrocyte sedimentation rate), procalcitonin
11. Serum cytokine levels (IL1, IL6,TNF, TNFR1, REG3 alpha, ST2) (Samples to be drawn and stored for later analysis)

7.0 REQUIRED DATA

7.1 Pre-Study Testing Intervals

To be completed within 30 DAYS before infusion of stem cells:

- All bloodwork
- History and physical
- bone marrow

All others to be completed within 42 DAYS before infusion of stem cells:

Tests & Observations on patient	Prior to infusion of stem cells	Day 0-Day 60	Beyond day 60 (only if evidence of donor chimerism)
Informed Consent	X		
History and Progress Notes	X	A ☻	E
Physical Examination	X	A ☻	E
Height	X		
Weight/Body Surface Area	X		
Karnofsky Performance Status	X		E
Drug Toxicity Assessment		B	
GVHD/Engraftment Syndrome assessment		B	E
Laboratory Studies			
CBC, Differential, Platelets	X	A	E
Serum Chemistry **	X	B	E
Uric Acid	X		E
Magnesium	X		E
PT (INR), PTT, Fibrinogen	X		
Urinalysis	X		
EBV PCR	X	B	E
CMV PCR	X	B	
Lymphocyte subsets (laboratory tests 17603138 and 17603144)	X	D	E
Chimerism Peripheral Blood	X	C	E
ESR, CRP, procalcitonin	X	D	E
HLA antibodies	X		F
CMV antibody test, hepatitis panel (HepA Ab, HepB Sab, HepB Sag, HepB Core Ab, HepCAb), herpes simplex, syphilis, HIV and HTLV 1 antibody, and varicella zoster virus	X		
Chest x-ray or Chest CT	X		
Staging			
Bone Marrow Asp,biopsy with cytogenetic and Flow and chimerism†	X***	Before day 60	
Correlative Laboratory studies			
Microchimerism*		C	E
Serum Cytokine level ((IL1, IL6,TNF, TNFR1, REG3 alpha,	X*	D*	E*

Tests & Observations on patient	Prior to infusion of stem cells	Day 0-Day 60	Beyond day 60 (only if evidence of donor chimerism)
ST2) (sample stored for subsequent analysis)			

† A bone marrow biopsy is required for response assessment in the event of a dry tap or an aspiration that is inadequate for interpretation.

A: At least twice weekly.
B: At least weekly starting on day of infusion
C: Weekly until day 60. Every two months thereafter until one year after cell infusion.
D: Every two weeks until Day 60. Lymphocyte subsets are performed only at Day 28.
E: At least monthly until Day 180 and at least every two months thereafter until one year. Lymphocyte subsets are performed only at Day 100, Day 180, and 1 year.
F: Performed only at Day 100 ☻ Physical exam and history will focus on signs and symptoms of GVHD
*microchimerism assays will be performed in selected cases of CBU infusion and based on HLA type of recipient, CBU unit and Mother of the CBU donor.
**Serum chemistry to include BUN, creatinine, electrolytes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, calcium, glucose, total protein, and albumin.
***Not required for subjects with ≥ 10% circulating peripheral blasts observed on manual differential.

7.2 CBU Graft Evaluation and Preparation Prior to Infusion:

Upon thawing and prior to infusion, CBU will be evaluated by

- Viability testing (including 7AAD, CFU)
- Cell Subset determination including at least CD3, CD34 –consider CD19, CD4, CD8
- CBUs will be washed prior to infusion.
- Sample for microchimerism (selected cases, based on maternal and fetal HLA type)

7.3 Haplo Donor and Product Evaluation Prior to Infusion.

Haplo donor evaluation will follow the routine transplant program policies. This will include screening for COVID (PCR test) as stipulated in Transplant Policies.

Haplo product may be infused fresh, after washing, or using bedside thaw.

The haplo product will be evaluated:

- At the time of collection using:
  - Cell subset determination including at least CD3, CD34,- consider CD19, CD4, CD8
  - Viability testing including Trypan Blue.
- At the time of cell infusion using
  - Viability testing (including 7AAD, CFU)

- Cell subset determination including at least CD3, CD34.

7.4 Response Assessment

A bone marrow examination to document response must be performed in all patients on or before Day 60. Physicians should consider earlier bone marrow exams in patients whose peripheral blood counts are not recovering or recovering sluggishly. Subsequent treatment (consolidation, salvage therapy, etc) will be at the discretion of the treating physician.

Patients will continue to be followed for survival, and disease status. Samples for correlative studies will be collected, if possible at 2 month intervals after day 60, until one year after treatment.

8.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, and electrocardiographs.

8.1 Investigational Risks

The investigational component of the study is the infusion of allogeneic cells. The possible complication of such treatment would be the development of severe GVHD and/or prolonged myelosuppression. The chemotherapy preceding adoptive cell therapy has numerous side effects and possible complications, but these are not considered investigational risks since the chemo is standard of care.

8.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment
  - Probable – The AE *is likely related* to the study treatment
  - Possible – The AE *may be related* to the study treatment
  - Unlikely – The AE *is doubtfully related* to the study treatment

- Unrelated – The AE *is clearly NOT related* to the study treatment

8.3 Recording and Reporting of Adverse Events and SAEs

- Safety reporting will be 21 CFR 312.32 compliant.
- Salvage chemotherapy for AML/MDS is a complex procedure with the possibility of prolonged initial admission and numerous immediate and delayed complications as well as frequent readmissions.

- **<u>Expected toxicities are those listed in the consent form</u> and include regimen-related toxicities, myelosuppression, opportunistic infections, haplo-immunostorm, engraftment syndrome and GVHD. These will be captured in the transplant database and reported to the IRB on a quarterly basis**

- **Unexpected** adverse events are those leading to ICU admission or to death. Such toxicities will be reported immediately to the designated study chairman. Such events will be reported to the local IRB within the institution's prescribed time period.

	Immediate Reporting	Report quarterly
Hematopoietic Toxicity	Death	Time to Hematopoietic recovery
Extramedullary Toxicity	Fatal toxicity and toxicity requiring ICU admission	Grade III-IV toxicities not requiring ICU admission
Infections	Fatal or requiring ICU admission	Grade II-IV
Acute GVHD	Fatal or Grade IV	Grade II-IV
Chronic GVHD	Fatal or requiring ICU admission	Limited and extensive
Haplo-immunostorm and/or engraftment syndrome	Fatal or requiring ICU admission	All others.

9.0 CRITERIA FOR STUDY EVALUATION

- Responses must be maintained with no evidence of AML/MDS for more than four weeks. If chemotherapy continues, there can be no evidence of relapse within four weeks. Response assessments will require a bone marrow aspirate to be performed. In the event of a dry tap or an aspiration that is inadequate for interpretation, a bone marrow biopsy is required for response assessment.

- **<u>Complete Remission (CR):</u>** Complete remission is defined as all of the following:

    - Peripheral Blood Counts:
        - Absolute neutrophil count ≥ 1000/μL
        - Platelet count ≥ 100,000/μL

        - No leukemic blasts in the peripheral blood
        - Adequate erythroid recovery so that RBC transfusions are not necessary

    - Bone Marrow:
        - Adequate cellularity
        - No Auer rods
        - < 5% blast cells

    - No extramedullary leukemia (such as CNS or soft tissue involvement)

    OR

    - Complete Response with Incomplete Platelet Recovery (CRp): CRp satisfies all CR criteria except platelets < 100,000/μL, but platelet transfusions are not necessary

- **Partial Remission (PR):** Must meet all criteria of a CR except that the bone marrow may contain 5%-24% blasts

- **Treatment Failure:** Failure to achieve a CR (by 60 days after initial induction therapy started)

    - Treatment Failure Due to Resistant Disease:
        - Patients treated appropriately
        - Survived > 30 days after therapy began.
        - Failed to achieve remission due to persistent AML as determined by peripheral blood and bone marrow aspirate and biopsy.

    - Treatment Failure Due to Death of the Patient:
        - Patient died within 30 days of starting protocol therapy.
        - Record whether the patient died with or without evidence of persistent leukemia as determined by peripheral blood and bone marrow aspirate and biopsy.

- **Relapse** - Any of the following, occurring after either CR, CRp, or PR:

    - The reappearance of circulating blast cells not attributable to "overshoot" following recovery from myelosuppressive therapy

    - > 5% blasts in the marrow, not attributable to another cause (e.g., CSF, bone marrow regeneration)

    - Development of extramedullary leukemia

- **Toxicities will be followed using CTCAE criteria.**
  Most toxicities will be attributable to the chemotherapy. Toxicity attributed to the cell infusions may include occurrence of GVHD and unexpected duration of myelosuppression. Severity of myelosuppression (hematologic toxicity) will not be taken into account.

- **Time to neutrophil recovery:**
  The first of three consecutive days with ANC >5x10^9/L.

- **Time to platelet recovery;**
  Platelet recovery is reported when the platelet count is $\geq 20 \times 10^9$/L seven days after platelet transfusion and is maintained for three consecutive lab values obtained on different days.
- **Treatment Related Mortality**
  Considered any death that cannot be explained by persistence, relapse or progression of the underlying malignancy once the preparative regimen starts.

- **Acute GVHD**
  Acute GVHD will be scored according to the criteria proposed by Przepiorka et al.[28]
  Risk score for acute GVHD will be further assigned based on recent publication by Mac Millan et al.[29]
  Chronic GVHD will be scored according to the consensus criteria.[30]

10. STATISTICAL CONSIDERATIONS

The primary objective of this study is to evaluate the safety of adoptive immunotherapy with IPA targeted CBU or with haplo-identical stem cells after conventional induction therapy for very high risk AML or MDS.

The study has 2 cohorts. Patients in cohort 1 will receive CBU cells as adoptive immunotherapy. Patients in cohort 2 will receive haplo identical cells. Both cohorts will be evaluated separately and no formal statistical comparison between cohorts will be performed in this pilot study.

Reinduction therapy in patients with recurrent AML and MDS is extremely toxic with high induction related mortality, which is however justified by the dismal prognosis of patients who don't receive treatment. Safety of the adoptive immunotherapy will be defined as absence of life threatening complications attributable to the adoptive immunotherapy part of the protocol. These are restricted to: 1) grade III-IV GVHD; an incidence of >10% of this complication in either cohort will be considered unacceptable. 2) Unexplained prolonged myelosuppression, i.e. no count recovery for more than 30 days after completion of chemotherapy, without evidence of residual or recurrent leukemia/MDS. An incidence of >10% of this complication will also be considered unacceptable.

10.1 Sample Size Considerations

With a sample size of approximately 20 patients in each cohort, a 95% confidence interval for the proportion of patients experiencing grade III-IV GVHD complications or unexplained prolonged myelesuppression complications in each cohort can be constructed to be within ± 13.1% of the observed complication proportions. This calculation assumes an expected prevalence of each of these complication proportions of ≤10%.

Addendum November 2017 Extension of the UCB cohort

The preliminary results in the UCB cohort are encouraging (section 2.6). We therefore have increased accrual to this cohort to a total of **35 patients treated**. This will allow a preliminary assessment of efficacy. Patients who are enrolled but do not undergo treatment (defined as infusion of stem cell product) will be replaced.

Addendum May 2020: In order to further solidify outcomes in the CBU cohort and pending completion of next protocols, we will further increase accrual to this cohort to a total of **60 patients treated**. This will allow a definitive assessment of efficacy. Patients who are enrolled but do not undergo treatment (defined as infusion of stem cell product) will be replaced.

10.2 Stopping Rules

The occurrence of adverse events that are life-threatening, lead to ICU admission or death (as defined in section 8.3) will lead to temporary suspension of enrollment and immediate assessment of events.

The study will also be paused if there is death that is directly attributed to infusion of adoptive cell therapy; for example severe infusion related reaction, infection from contaminated unit, Grade 5 GVHD etc.

Enrollment may resume upon assessment by the investigators that there are no safety issues and upon appropriate revision of the protocol – if required.

After 10 patients are enrolled in each group, the incidence of the above-defined life-threatening complications will be assessed. If more than one patient out of 10 enrolled patients (i.e., >10%) in a cohort experiences either of these complications, the cohort will be stopped for safety. Each cohort will be evaluated separately with respect to these complications. Additionally, if three or more of the first five patients in a particular cohort experiences either of these complications, the cohort will also be stopped. This is illustrated in the Table below.

N treated subjects	5	10	15	20
No with gr III-IV GVHD to trigger stopping rules	2	2	3	4
No with prolonged myelosuppression to trigger stopping rules	2	2	3	4
No with either Gr III-IV GVHD or with prolonged myelosuppression to trigger stopping rules	3			

For assessment of secondary objectives, descriptive statistics will be utilized via the method of binary proportions and 95% confidence intervals will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.3 (SAS Institute, Inc., Cary, NC) and Stata Version 13.0 (StataCorp, College Station, TX).

Addendum 5/26/2020: To date stopping rules have not been met in the CBU cohort after enrolling more than 30 patients. The Haplo cohort has not accrued.

10.3 Screening vs Treating

We anticipate that several patients will be consented and then screened for each patient treated. The sample sizes are based on number of patients treated – not on number of patients consented.

11. CRITERIA FOR REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

11.1 Duration of Treatment

Patients will continue with the therapy specified in this protocol until one of the following occurs:

- Achievement of protocol endpoint CR or CRp after induction and cellular therapy
- Failure to achieve CR or CRp
- Extraordinary Medical Circumstances: If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, remove the patient from protocol treatment. In this event.

After removal from protocol therapy, patients will continue to be followed for survival and disease status. Samples for correlative studies will continue to be collected every two months until one year after cell infusion.

12. DATA, SAMPLE AND PROTOCOL MANAGEMENT

- **Protocol Compliance:** Patients will be reviewed weekly during admission by the Study Investigators who will score the patient for standard endpoints.
- **Data Entry:** REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

- **Accuracy of Data Collection:** The Study Chairman will be the final arbiter of toxicity should a difference of opinion exist

- **Management of Research samples:** Research samples will be cryopreserved after ficolling and isolation of viable cells. The serum will be stored separately. Part of the product may be stored after DNA extraction. The samples will be stored securely. They will coded with the key to identification of the samples kept in a secure location and available only to the PI or his delegate. Samples and appropriate clinical information may be shared with other investigators at WCMC and elsewhere, but will be de-identified. Samples will be kept indefinitely.

13.0 DATA SAFETY MONITORING BOARD

The Weill Cornell Medical College Data Safety Monitoring Board (DSMB) is being requested to review safety data and to make recommendations regarding continuation, termination, or modification to the study.
The research team will report all adverse events to the DSMB after accrual of successive sets of five patient to each arm of the protocol. The report to the DSMB will include a description of adverse events attributed to cell infusion and of patient's outcome.

14.0 REGULATORY CONSIDERATIONS

14.1 Institutional Review Board/Ethics Committee Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted for approval by the Investigator to the IRB/EC. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

14.2 Informed Consent Procedures

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedure as per GCP's as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. At the pre-admission consultation, patients will be fully informed as to the purposes and potential risks and benefits involved in this study. Patients will have ample opportunity to ask questions before consenting. Legal guardians will sign informed consent for legally incompetent patients in accordance with hospital policy.

14.3 Protecting Privacy and Confidentiality

Confidentiality will be maintained within the limits of the law. Patient names or any other identifying information will not be used in reports or publications resulting from this study. Only qualified staff from New York Presbyterian Hospital, Weill Medical College of Cornell University, the Food and Drug Administration, or other study support such as the National Cancer Institute will be able to review patient medical records.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.4 Study Records Requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

14.5 Protection of Human Rights

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to Weill Cornell Medical College IRB guidelines.

Patients will be eligible for this trial regardless of gender or racial/ethnic background.

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