A Phase II Clinical Trial of "Off-the-shelf" NK cell administration in combination with allogeneic SCT to decrease disease relapse in patients with high-risk Myeloid malignancies undergoing Matched related, Matched unrelated, One antigen mismatched unrelated, or Haploidentical Stem-cell Transplantation

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Principal Investigator: Jeremy Ramdial, MD
The University of Texas MD Anderson Cancer Center
Stem Cell Transplantation and Cellular Therapy Department
1515 Holcombe Blvd, Unit 0423
Houston, TX 77030
Telephone: 713-745-0146
Fax: 713-794-4902
jlramdial@mdanderson.org

Co-Chairs: Richard Champlin, MD[1]

Collaborators: Bouthaina S. Dabaja, MD[2]
Peter Thall, PhD[3]
Roland L.Bassett, Jr., MS[3]

[1] The University of Texas MD Anderson Cancer Center, Stem Cell Transplantation and Cellular Therapy Department
[2] The University of Texas MD Anderson Cancer Center, Radiation Oncology Department
[3] The University of Texas MD Anderson Cancer Center, Biostatistics Department

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1.0 Objectives

1.1 Primary Objective

Assess the safety and effectiveness of “off the shelf” third party NK cells in combination with allogeneic SCT in patients with myeloid malignancies.

1.2 Secondary Objectives

i. To assess NK cell related toxicities
ii. To estimate the proportion of patients with engraftment/graft failure.
iii. To assess the rate of leukemia relapse, disease-free survival (DFS), overall survival (OS), and GVHD-free, Relapse-free survival (GRFS) after transplantation by one year.
iv. To estimate the non-relapse mortality (NRM) at day 100, day 180 and 1 year post-transplant.
v. To estimate the cumulative incidence of grade 2-4 and grades 3-4 aGVHD at day 100.
vi. To assess the rate of chronic GVHD within the first-year post transplantation.
vii. To assess rate of BK, CMV, and Adenovirus infections.
viii. To assess MRD.
ix. To assess immune reconstitution post-transplant.

2.0 Background and Rationale

2.1 AlloSCT for AML, MDS, and TKI resistant/intolerant CML

Acute myeloid leukemia, myelodysplastic syndrome, and TKI resistant CML continue to be among the most aggressive forms of blood cancer. Allogeneic hematopoietic stem cell transplantation (alloSCT) remains one of the most effective treatments available. Much of the benefit of AlloSCT is due to the immune-mediated graft-versus-leukemia effect to prevent relapse[1-4]. Nevertheless, disease relapse remains the most important cause of treatment failure after alloSCT.

A potential solution to reduce the risk of relapse may be found in Natural Killer (NK) cells, which have a demonstrable ability to eliminate leukemic and virally infected cells. However, naturally produced NK cells seen in patients early post-transplant are functionally impaired. A potential solution would be to provide donor-derived, expanded and activated NK cells in the peri-transplant setting. This is a challenge, since patients have aggressive disease characteristics and patient-specific donor NK cells require a substantial time to expand, donor NK cells from the same donor as the stem cell donor may not confer optimal anti-leukemic

reactivity, and patient specific manufacture of NK cells is expensive.

Administration of off-the-shelf third party NK cells in the peri-transplant period may allow for minimizing delays in treatment and also provide the benefit to select a donor conferring effective NK cell alloreactivity to enhance the graft versus leukemia effect and decrease relapse. Large numbers of expanded NK cells may be produced from one donor improving cost effectiveness.

2.2 Natural Killer Cells

Natural killer (NK) cells are a unique class of lymphocytes, with cytotoxic, and immunoregulatory function which can mediate potent antileukemia effects[5-7]. NK cells are regulated by Killer-cell Immunoglobulin-like Receptors (KIR) receptor-ligand interactions and mediate cytotoxicity against certain HLA class I mismatched targets[8]. Alloreactive NK cells have been reported to enhance engraftment, reduce GVHD and prevent relapse of leukemia post transplant[5-7]. This study will utilize NK cells from third party donors as adjuvant treatment to eradicate leukemia and prevent disease relapse after transplantation.
Natural killer cells have both cytotoxic and immunoregulatory functions. Human NK cells are characterized by expression of CD56 with or without CD16, and the absence of T-cell receptor and CD3 expression[5,6]. There are 2 subtypes of NK cells: $CD56^{dim}CD16^{bright}$ cells, which compose 90% of the NK cells from circulation which have cytotoxic function, and express MHC class I allele-specific KIRs, and the $CD56^{bright}CD16^{neg}$ cells present in small numbers in the peripheral blood but 100% in lymphoid tissues, and secrete immunoregulatory cytokines, like interferon (IFN) gamma, and promote adaptive immune responses. NK cell cytotoxicity can be upregulated by increased secretion of cytokines including interleukin (IL)-2 (IL-2) and IL-15, whereas IL-12 and IL-18 increase IFN-γ secretion by NK cells[5]. NK cell reactivity is governed by activating and inhibitory receptors. By the “missing ligand model” initially described by Karre in 1986, killing of tumor cells by NK cells occurs when there is a missing signal (or missing self) on the target cells[9]. Several inhibitory receptors and putative activation receptors of the NK have been characterized and they can be classified as lectin-like receptors (CD94) receptors and KIR[10-12].

In man, some HLA class I molecules expressed on the target cells are ligands of the CD94 and KIR receptors. The interactions between NK receptors molecules are specific for different HLA isotypes, for example, the inhibitory receptor KIR2 DL4 interacts with HLA-G molecules. KIRs interact with groups of alleles of HLA-C and HLA-B. It is of interest that the KIR2DL1 receptor interacts with alleles of the HLA-C locus that have the amino acid lysine (Lys) at residue 80 (C-lys-80) while the receptors KIR2DL2 and KIR2DL3 interact with alleles of HLA-C that have asparagine (Asn) at residue 80 (C-asn-80). Interestingly, the substitutions Lys/Asn at residue 80 define a bi-allelic system in all alleles of HLA-C in which all the alleles of this locus carry either of these amino acids. The alleles of HLA-B locus present also different capacities to interact with the receptor KIR3DL1; only the HLA-B

alleles carrying the supertypic serologic epitope HLA-Bw4 (encoded in the amino acid stretch spanning residues 77-83) interact with KIR3DL1[10-12]. Therefore, in an allogeneic transplantation setting, in which the donor and recipient are mismatched in the alleles of HLA-B or in HLA-C, the NK cells from the donor may not be inhibited by the target cells of the recipient that lack the appropriate HLA alleles which interact with the KIR receptors.

In allogeneic bone marrow transplants the graft-versus-leukemia effect has been attributed in part to NK cells not being uninhibited due to the lack of the appropriate HLA ligand in the recipient. It is important to note that the KIR genes are encoded as a haplotype block (KIR loci) on chromosome 19q. The KIR haplotypes differ in gene content between individuals and some individuals may lack some KIR genes. The NK repertoire therefore may vary from individual to individual and will depend on the HLA phenotype and in the KIR haplotype gene composition.

Allogeneic stem cell transplantation confers an immune mediated graft-vs.-leukemia effect. NK cells have been shown to mediate a potent antileukemia effect against myeloid leukemias. As indicated above, inhibitory KIRs recognize HLA-C and -Bw antigens, when the corresponding ligand (HLA molecule) is present, cytotoxicity is inhibited; when the ligand is absent, cytotoxicity occurs (based on the “missing ligand” principle)[13]. Thus, NK cytotoxicity is most marked when NK cells react against a target missing the relevant class of HLA class I molecules. Velardi et al. have studied the results of T-cell depleted haploidentical transplants from alloreactive or nonalloreactive donors based upon this “missing ligand” principle[14], and demonstrated that patients predicted to have alloreactive NK cells had no relapses compared to a 75% relapse in recipients of nonalloreactive transplants[15].

2.3 Clinical experience using infusion of NK cells after transplant

Several lines of evidence suggest that increased numbers of alloreactive NK cells would have benefit in the transplant setting, despite the fact that retrospective results vary depending on patient population, underlying diseases, conditioning regimens, graft composition and cell dose, degree of T-cell depletion, post-transplant immunosuppressive regimens and differing methods of determining alloreactivity[16]. Ruggeri et al. reported a retrospective evaluation of NK alloreactivity in transplanted patients[15] and supportive NK models. This group analyzed 92 patients with high risk leukemia who received a haplotype mismatched hematopoietic stem cell transplant (HSCT) and reported that NK cell alloreactivity improved engraftment, protected from graft-versus-host disease (GVHD) and reduced the rate of relapse[17]. In mouse xenograft models it was demonstrated the role of alloreactive NK cells in eradicating human leukemia, improved engraftment by targeting host T lymphocytes, and reduced GVHD by eliminating recipient-type dendritic cells[18]. In addition, the NK cell dose of the infusion product has been associated with better outcomes following matched sibling transplants[19].

Table 1. Clinical studies using adoptive NK cell immunotherapy after hematopoietic stem cell transplantation.

First author	Disease and # of treated patients	Type of transplant (n)	Median NK cell dose infused	Method of generation of NK cell product	Phase of clinical trial	aGVHD Y/N	Response/outcome
Koehl	AML (1), ALL (4), HD (1), RMS (1)	Haplo (7)	N/A	Unstimulated leukapheresis, CD3 depletion and CD56 selection, IL2 activation	I	Y (3 pts)	5/7 patients were alive in CR 4-13 months post SCT
Passweg	AML (4), CML (1)	Haplo (5)	N/A	Unstimulated leukapheresis, CD3 depletion and CD56 selection	I	N	3/5 pts were alive and CR 18-36 months after NK infusion
Slavin	MDS (2), AML (1), ALL (1), biphenotypic (1), HD (1); NHL (2).	Haplo (3) MRD (4) MUD (1)	2.1x106/kg	CD56 selection from rIL-2 activated lymphocytes	I	N	One pt with relapsed ALL and one with MDS had CR. 4 pts alive, 3 disease free 9-22 month post SCT.
Barkholt	Solid tumors (4), CLL (1)	MRD (5)	13.2x106/kg	Expanded NK cells and NK cell-like T cells	I	N	CLL patient progressed
Uharek	AML (16), ALL (5), CML (2), HD (1), MDS (1)	Haplo (25)	9.6x106/kg	NK cells isolated from CD34- cell fraction; CD3 depletion and CD56 selection	I/II	Y (4 pts)	9/25 patients alive and in CR, with 2-year OS of 29%
Rizzieri	30 patients with myeloid and lymphoid malignancies	Haplo (16) MRD (14)	10.6106/kg	Unstimulated leukapheresis enriched in NK cells using CD56 antibody	I/II	Y (14 pts, 6 /14 had grade I skin aGVHD)	Total of 16 patients in CR with 1 year OS of 43% and 42% of matched and mismatched respectively

Legend: MRD – matched related donor transplant; MUD – matched unrelated, Haplo – haploidentical transplant, AML – acute myeloid leukemia, ALL – acute lymphoblastic leukemia, HD – Hodgkin's disease, RMS – rhabdomyosarcoma, CML – chronic myeloid leukemia, MDS – myelodysplastic syndrome, NHL – non-Hodgkin's lymphoma, CLL – chronic lymphocytic leukemia; Y – yes, N – no; GVHD – graft-versus-host disease. (Adapted from Farhan S, et al. NK cell therapy: targeting disease relapse after hematopoietic stem cell transplantation. Immunotherapy. 2012;4:305.)

A number of small prospective studies published mostly in abstract format (listed in Table 2), have reported on the safety of NK cell infusion. This experience has been recently reviewed by us[6]. A study of patients infused with NK cells post-transplant was reported by the Duke University group on non-expanded NK cells[20]. They infused a total of 51 NK cell-enriched donor lymphocyte infusions (DLIs) to 30 patients following a 3-6/6 HLA matched T-cell-depleted non-myeloablative allogeneic transplant using with alemtuzumab part of the conditioning regimen[20]. Eight weeks following transplantation, donor NK cell-enriched DLIs were processed using a CD56+ selecting column, with up to 3 fresh infusions allowed. Fourteen matched and 16 haploidentical transplant patients received a total of 51 NK cell-enriched DLIs. The median number of CD3- CD56+ NK cells infused was 10.6×10^6 cells/kg and 9.21×10^6 cells/kg for matched and mismatched, respectively. The median number of contaminating CD3+CD56— T-cells infused was 0.53×10^6 and 0.27×10^6 cells/kg in the matched and mismatched setting, respectively. All but 2 subjects had donor engraftment accounting for >80% of their hematopoiesis at the time of first infusion. After a median follow-up of 12 months for matched sibling donor transplants, and 27 months for the haploidentical transplants, 1 year overall survival was 43% and 42%, respectively[18]. Evaluating outcomes by disease, 1-year survival was 50% for the 19 patients with myeloid

diseases 29% for patients with lymphoid diseases. Only 1 patient each in the matched (n=14) or mismatched (n=16) groups experienced severe aGVHD with little other toxicity attributable to the infusions. Importantly, long-term responders had improved T-cell phenotypic recovery and improved duration of responses and overall survival after multiple NK cell-enriched infusions[20].

Finally, our group showed feasibility and safety of infusing high doses of ex vivo–expanded NK cells after haploidentical HSCT without adverse effects, increased GVHD, or higher mortality, and was associated with significantly improved NK-cell number and function, lower viral infections, and low relapse rate posttransplant[21]. No infusion reactions or dose-limiting toxicities occurred. All patients engrafted with donor cells. Seven patients (54%) developed grade 1-2 acute GVHD (aGVHD), and in later follow-up one developed grade 3-4 aGVHD and one developed chronic GVHD[22], and a low incidence of viral complications was observed. One patient died of nonrelapse mortality; 1 patient relapsed. All others were alive and in remission at last follow-up (median, 14.7 months). NK-cell reconstitution was quantitatively, phenotypically, and functionally superior compared with a similar group of patients not receiving NK cells.

2.4 Rationale for use of third party expanded NK cells

Kiadis Pharma is developing natural killer (NK) cells for oncologic therapeutic indications. KDS-1001 is an off-the-shelf donor-derived NK cell investigational immunotherapy manufactured with donor material obtained from an allogeneic donor. The expected efficacy and safety of KDS-1001 is derived from the known efficacy and safety profile of NK cells expanded using mbIL-21 and 4-1BBL expressing feeder cells. FC21-NK cells continue to be used worldwide in clinical trials in various tumor indications (See below).

NK cells produced by utilizing the FC21 platform are used in multiple clinical trials in adults and pediatric population (Table 2). Three phase 1 clinical trials have been completed in adults: NCT0172909119, NCT0190413620, and trial NCT01823198 in myeloid malignancies (unpublished, 22 patients). Upon positive outcomes of the phase 1 parts, two of these studies (NCT01729091 and NCT01904136) continued with a phase 2.

Following the promising results in the phase 1 trials, FC21-NK cells are currently being used in 5 ongoing trials in pediatric and adults patients with:
- relapsed/refractory AML - NCT0178747423
- relapsed/refractory AML - NCT0280909224
- relapsed/refractory AML - NCT0422068425
- solid tumors including hepatocellular carcinoma - NCT02008929
- non-small cell lung cancer - NCT02370017

In addition to these trials, feeder cell expanded NK cells are being utilized in pediatric trials treating solid tumors such as neuroblastoma (NCT02573896, NCT03242603 and NCT03209869) and brain tumors (NCT0227171126).

Published (interim) efficacy and safety results for these studies are summarized in Table 2.

Table 2 Overview of Clinical Studies with mbIL-21 and 4-1BBL Feeder Cell Expanded NK Cells

Study information	Study population (#pts with results)	Type, expansion dose and #doses	(Interim) Efficacy results	(Interim) Safety results
Shah 2017[19] NCT01729091 completed	12 adult MM pts undergoing autologous transplantation	allogeneic 5×10^8 to 10^8/kg 1 dose	10 pts achieved at least a very good PR, including 8 with near CR or better.	No infusion related toxicities and no GVHD
Shah 2018[21] NCT01729091 ongoing	33 adult MM pts undergoing autologous transplantation	allogeneic 5×10^7-10^8/kg 1 dose	Responses at 3 months: CR:55%; VGPR: 12%; PR: 21%. Best response was CR: 65%; VGPR: 18%; PR: 9%.	No toxicities associated with the NK cell infusions. 54% pts developed grade I/II aGVHD, no grade III/IV aGVHD or cGVHD. 1 pt died of NRM; 1 pt relapsed.
Ciurea 2017[20] NCT01904136 completed	11 adult AML/MDS pts receiving haploidentical HSCT	Allogenic 10^5 - 10^8/kg 3 doses	Primary engraftment 100%. Remission: 82%, relapse 9%. NRM: 9%. CMV reactivation: 30.8% NK cells pts vs. 70.4% for control. BKV: 7.7% NK cell pts vs. 31.8% for control;	No infusion-related reactions or dose-limiting toxicities occurred.
Ciurea 2020[22] NCT01904136 completed	13 adult AML/MDS pts receiving haploidentical HSCT	Allogenic 10^8/kg 3 doses	Increased DFS, OS, and NRM. Relapse rate: 4% NK cell pts vs. 38% for controls	No infusion reactions or significant adverse events related to the NK cells. aGVHD (all grades): 42% NK cell pts vs 36% controls. aGVHD (III/IV) 4% NK cell pts vs 15% controls; cGVHD 0% vs 44% controls
Ciurea 2018[23] NCT01787474 ongoing	13 pediatric/ adults pts with AML/MDS/CMML	allogenic 10^6-5×10^6 6 doses	Responders: 69%, Partial responders: 23%, Non-responder: 8%	One patient with pre-existing liver toxicity developed worsening hepatic dysfunction and died.
Silla 2020[24] NCT02809092 ongoing	4 pediatric/adults pts with R/R AML and CNS disease	autologous 10^6- 10^7/kg, 6 doses	CR: 50%, CR(i): 25%, PR: 25%	No dose-limiting toxicities. Other toxicities were manageable, including CNS hypertension symptoms.
Khatua 2019[26] NCT02271711 ongoing	7 pediatric pts with brain tumors	escalating dose, 3 doses	2 responders,5 non-responders	No safety results reported

aGVHD = acute Graft versus Host Disease; AML= acute myeloid leukemia; BKV = BK virus; cGVHD = chronic Graft versus Host Disease; CMML = Chronic myelomonocytic leukemia; CMV = cytomegalovirus; CR=complete response; DFS = disease free survival; HSCT= hematopoietic stem cell transplantation; IL= interleukin ; MDS = myelodysplastic syndrome; MM = multiple myeloma; NK = natural killer; NRM = non-relapse mortality; OS= overall survival; PR = partial response; pt(s) = patient(s); PFS = progression free survival; VGPR = very good partial response.

There are several limitations to patient specific donor-derived, expanded NK cells. The cells must be manufactured from individual donors at great expense and take approximately one month to produce. This process requires an extra visit from the donor. Available donors may not have the optimal HLA and KIR genes to generate optimal anti-leukemic activity. Additionally, the inevitable possibility of failure in manufacturing of patient-specific therapeutics would leave patients without an alternate source of NK cells.

An alternate is to produce expanded NK cells from selected third-party donors. Such cells would be banked and could be immediately available and be selected to confer maximal alloreactivity against the patient's leukemia.

We have shown that 10^8 expanded third party NK cells/kg can be safely infused with an autologous stem cell transplant and not produce graft failure or GVHD[23]. Similarly $1x10^8$ NK cells per kg, third party cord blood derived NK cells can be infused on day -2 prior to allogeneic transplantation from HLA matched unrelated donors for treatments of myeloid leukemias without graft failure or an increase in the expected rate of acute GVHD[20]. In both of our studies the rate of relapse of the malignancies was low.

In this study, we will examine the safety and potential efficacy of third party ex vivo expanded NK cells administered as adjunctive therapy to allogeneic HSCT with the goal of preventing leukemia relapse. Doses up to 10^8 NK cells/kg have been safely used in the aforementioned studies. This study will administer $3x10^7$ NK cells/kg as a feasible dose to produce for therapeutic purposes (NK cells may be formulated

so that actual dose administered is +/- 20%) [Weight-based dosing bands]. If a patient's weight exceeds 125 kg, the patient will receive the dose for a 125 kg patient).

2.5 KDS-1001 description

The investigational product for this study is K-NK cells that will be manufactured and packaged by Kiadis Pharma Netherlands B.V. (Kiadis Pharma). This product is referred to as KDS-1001.
KDS-1001 is composed of NK cells from a universal donor, expanded ex vivo using PM21 membrane particles. PM21 particles are formed from the plasma membranes of K562.mbIL21.41bbl (CSTX002) feeder cells.
KDS-1001 is an NK cell suspension for intravenous administration and will be supplied frozen in cryobags, formulated at 5 x 10^7 viable NK cells/mL.

2.6 KDS-1001 Nonclinical experience

In comparative in vitro studies, PM21 membrane particles effectively stimulated expansion of NK cells at rates similar to methods using feeder cells expressing mbIL-21 and 4-1BBL (FC21) and expressed the expected NK cell activation and inhibitory surface receptors, including the receptors NKG2D, NKp46 and CD16. PM21-NK cells and FC21-NK cells showed similarly potent cytotoxic activity against human leukemia target cells at relatively low effector concentrations. Likewise, PM21-NK cells and FC21-NK cells both secreted high amounts of anti-tumor cytokines upon stimulation with cytokines or K562 human leukemia cells. Finally, PM21-NK cells and FC21-NK cells displayed similar activity towards tumor cells in a transgenic cancer mouse model.
Refer to the IB, section 4, for the details from non-clinical in-vitro and in-vivo studies.

3.0 Patient Eligibility

3.1 Inclusion criteria

1) Patients ages 18 to 70 years old at the time of enrollment.
2) Patients weighing at least 42 kg
3) Patient with the hematologic malignancies described below, as well as an HLA matched related donor, HLA matched unrelated donor, a haploidentical related donor, or a one antigen mismatched unrelated donor. HLA matching includes HLA A, B, C, and DR-B1.
4) Patients must have one of the following diseases:
   <u>Acute myeloid leukemia (AML):</u>
   a. With one or more high-risk features defined as:
      (i) Greater than 1 cycle of induction therapy required to achieve remission;
      (ii) Preceding myelodysplastic syndrome (MDS);

(iii) Presence of FLT3 mutations or internal tandem duplication or other mutations designated as adverse-risk by the ELN Leukemia Net AML Classification (see Appendix 2):
Adverse:
- t(6;9)(p23.3;q34.1)/DEK::NUP214
- t(v;11q23.3)/KMT2A-rearranged#
- t(9;22)(q34.1;q11.2)/BCR::ABL1
- t(8;16)(p11.2;p13.3)/KAT6A::CREBBP
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1)
- t(3q26.2;v)/MECOM(EVI1)-rearranged
- *−5 or del(5q); −7; −17/abn(17p)*
- Complex karyotype,** monosomal karyotype††
- Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡
- Mutated TP53a

(iv) FAB M6 or M7 classification;
(v) Adverse cytogenetics: -5, del 5q, -7, del7q, abnormalities involving 3q, 9q, 11q, 20q, 21q, 17, +8 or complex karyotype [> 3 abnormalities]; or other mutations designated as adverse-risk by the ELN criteria;
(vi) Treatment-related AML
(vii) Primary induction failure with partial response to therapy who achieve adequate cytoreduction
(viii) Aplastic/hypoplastic marrow with or without detectable persistent disease after induction chemotherapy or after salvage chemotherapy.
(ix) Have minimal residual disease by flow cytometry, FISH, detection of disease related mutations or cytogenetic abnormality after first course of induction chemotherapy
(x) Have relapsed after prior allogeneic hematopoietic transplant

AND

b. Patients must be in one of the following
(i) CR: complete remission,
(ii) CRi: CR with incomplete hematologic recovery, or
(iii) MLFS: morphological leukemia-free state with less than 5% bone marrow blasts.
(iv) Primary induction failure with response to therapy who achieve adequate cytoreduction
(v) Aplastic/hypoplastic marrow without detectable persistent disease after induction chemotherapy or after salvage chemotherapy

Myelodysplastic syndromes (MDS):
a. De novo MDS with intermediate or high-risk IPSS scores, chronic myelomonocytic leukemia (CMML) or treatment-related MDS. Patients

with intermediate-1 features should have failed to respond to hypomethylating agent therapy. .
Patients must have less than 10% bone marrow blasts

Chronic myeloid leukemia (CML):

a. Failed to achieve cytogenetic remission or have cytogenetic relapse after treatment with at least 2 tyrosine kinase inhibitors, or
b. Accelerated phase or blast phase at any time, or
c. Intolerant of available TKIs

5) Performance score of at least 70% by Karnofsky or 0 to 1 by ECOG.

6) Adequate major non-hematopoietic organ system function as demonstrated by:
   a. Serum creatinine clearance equal or more than 50 ml/min (calculated with Cockcroft-Gault formula).
   b. Bilirubin equal or less than 1.5 mg/dL except for Gilbert's disease. ALT or AST equal or less than 200 U/L for adults. Conjugated (direct) bilirubin less than 2x upper limit of normal.
   c. Left ventricular ejection fraction equal or greater than 45%.
   d. Diffusing capacity for carbon monoxide (DLCO) equal or greater than 60% predicted corrected for hemoglobin.
7) Ability to understand and willingness to sign the written informed consent document.
8) Sexually active males and females of childbearing potential must agree to use a form of contraception considered effective and medically acceptable by the Investigator while on study.

3.2 Exclusion criteria

1) HIV positive; active hepatitis B or C.
2) Uncontrolled infections; PI is the final arbiter of this criterion.
3) Liver cirrhosis.
4) CNS involvement within 3 months prior to the transplant.
5) Positive pregnancy test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization.
6) Inability to comply with medical therapy or follow-up.
7) Patient with a known history of allergic reactions to any constituents of the product, including a known history of allergic reactions to cellular products or DMSO.
8) Other malignancy/cancer diagnosis with active disease or in remission and <2 years ago, not including nonmelanoma skin cancer
9) Requiring systemic corticosteroids with prednisone dose >10 mg or equivalent.
10) KDS-1001 Donor specific antibodies (dsa) >3000 MFI units or C1q positive

4.0 Evaluation During Study

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.

Evaluation During Study
Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule and occasional missed required research samples. Missed samples for correlative studies will not constitute protocol deviations. The following tests are standard of care pre-transplant tests and not protocol specific. The results are used to determine transplant eligibility and should not be repeated prior to the beginning of treatment, unless the treatment is delayed for more than 30 days after consenting:

- CBC, differential and platelets
- Bilirubin, serum creatinine and creatinine clearance, ALT, albumin, electrolytes, LDH, alkaline phosphatase
- Infectious diseases panel (hepatitis serology (B, C), HIV, HTLV, I/II, CMV, TPHA screen), toxoplasma serology,
- PT and PTT
- ABO and Rh typing
- Bone marrow aspiration and biopsy with cytogenetics, flow cytometry and molecular studies as clinically indicated
- Chimerism analysis baseline
- Serum pregnancy test in females of childbearing potential
- Pulmonary function test with DLCO
- Echocardiogram or multigated acquisition scan (MUGA) to assess Left ventricular EF
- Chest X ray and ECG
- Serum for donor-specific anti-HLA antibodies (DSA) if clinically indicated

Standard Post Transplant Evaluations
Patients will receive standard supportive care and monitoring as clinically indicated for allogeneic hematopoietic transplantation. Patient evaluations and testing follow our standard practice and are performed to monitor engraftment, identify and manage toxicities and infections, and to assess disease status:
1. Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells.
2. At each visit, a physical examination and adverse event documentation including GvHD assessment.
3. Transplant Panel from the peripheral blood T-cell subsets, B-cell immune reconstitution, +/- NK cell studies collected at same time as correlatives.

4. Disease specific assessment as per standard of care and SCT&CT guidelines including bone marrow aspirate with cytogenetics and molecular studies if clinically indicated.

Study staff will contact study participants regarding their health status once a year starting 12 months post 100 days post transplant.

Blood samples for correlative studies will be sent to Dr. Katy Rezvani's laboratory (located in Zeyad Building), Phone 713-563-1894, Pager: 713-404-3858).

A total of 2cc/kg up to 60cc will be required, 5 (10cc) green top tubes and 1 (10cc) purple top tube.

Sample collection for exploratory analyses
Exploratory analyses with immunophenotyping for NK cell chimerism and persistence will be done as feasible. Immune reconstitution studies or additional future research may be performed.

Time points for sample collection for immunophenotyping for detection of NK cells and immune reconstitution are relative to day of transplant (day 0) approximately: Day -7, Day -2 (2-6 hours post first KDS-1001 infusion), Day +3 (2-6 hours pre-cyclophosphamide), Day +7 (2-6 hours pre- KDS-1001 administration), Day +8, +14, Day +28 (2-6 hours pre-KDS-1001 administration), and then on Days +35, and +60.

Samples from bone marrow aspiration will also be studied at approximately day 28, day 90, and for bone marrow aspirations if performed for suspicion of relapse.

See Table 1 below for details.

Table 1. Schedule of Study Procedures and Assessments

	Baseline	Day -7	Day -2	Day 0	Day +2	Day +7 (±2 days)	Day +14 (± 5 days)	Day +21 (±5 days)	Day +28 (±5 days)	Week 5 (±5 days)	Week 6 (±2 wks)	Week 7 (±2 wks)	Week 8 (±2 wks)	Week 9 (±2 wks)	Month 3 (±2 wks)	Month 6 (±2 wks)	Month 9 (±2 wks)	Month 12 (±2 wks)
Informed consent	X																	
History, physical exam, (height weight at baseline)[1]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCT-Comorbidity Index	X																	
Karnofsky performance status	X								X						X	X		
CBC[2] differential, chemistry panel[3], LDH	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
KDS-1001 Administration			**X**			**X**			**X**									
Infusion-related toxicities			X			X			X									
Allogeneic SCT				**X**														
Donor-specific antibodies	X							X					X					
CMVPCR	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Adenovirus infection	X								X				X		X	X	X	X
Infection evaluation[4]	X																	X
Urine BK PCR[5]						X			X									
LVEF	X																	
DLCO, FEV1, FVC	X														X[11]			
Serum beta-HCG (females)[6]	X																	
Chest x-ray and ECG	X																	
Bone marrow aspirate, biopsy, flow cytometry, relevant cytogenetic and molecular studies[7]	X								X						X			X
GVHD assessments[8]						X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE assessments[9]			X	X	X	X	X	X	X	X	X	X	X	X	X			
Sorted chimerisms from blood[10]	X								X				X		X			
Transplant Panel									X				X		X			
Exploratory analyses (see previous page)		X	X (2-6 hrs post-KDS-1001)		X (D+3, 2-6 hrs pre cytoxan)	X (D+7 , -6 hrs pre- KDS-1001, & D+8)	X		X (2-6 hrs pre-KDS-1001)	X (Day +35)_			X (Day +60)					

[1] Physical exam at baseline, within 14 days prior to initiation of conditioning and end of treatment visit should include vital signs and a complete physical examination, to include assessment according to standard techniques of general appearance, head, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological, endocrine, dermatological and lymph nodes. Height and weight is required at baseline. It is not required to be repeated at the other time points. At all other times, physical exam may be performed at the investigator's discretion based on the patient's status.

[2] Patients are evaluated according to standard practice in support of hematopoietic transplantation. Evaluations generally include: CBC with differential performed three times weekly from Day 0 until ANC at least 500/mcL or greater for three days and platelet count at least 20,000/mcL or greater after nadir, while hospitalized. CBC then performed weekly through Day 63 post-transplant and then every other week until Day 100 post-transplant, then at Days 180, 270, and 365 post-transplant. Only those labs listed on the Summary of Required Clinical Assessments table for each visit will be captured in the eCRF; all other lab results obtained between study visits will be collected and maintained by the site as part of SOC. The actual dates of PLT and ANC engraftment will also be captured in the eCRF. CBC with differential needs to be collected and reported in CRF at all visits where research blood samples are collected for cryopreserved Biorepository samples to be used for future NK cell persistence studies.

[3] Blood chemistries include: serum creatinine, albumin, bilirubin, alkaline phosphatase, AST and ALT. Blood chemistries performed twice weekly until hospital discharge. Blood chemistries performed weekly after hospital discharge until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant. Only those labs listed on the Summary of Required Clinical Assessments table for each visit will be captured in the eCRF; all other lab results obtained between study visits will be collected and maintained by the site as part of SOC.

[4] Infectious disease assays should be performed per institutional guidelines. CMV shall be monitored per SOP as NK cells are derived from a CMV (+) donor

[5] Urine BK PCR can be done more frequently based on symptoms, or earlier based on institutional guidelines.

[6] Pregnancy test must be performed ≤ 14 days before the start of the transplant conditioning regimen. Pregnancy test is required for females of child-bearing potential and may be performed per institutional practices.

[7] Evaluation of disease: (A) For acute leukemia MDS, evaluation for malignant disease includes a bone marrow aspirate and biopsy for histology and cytogenetics. **A bone marrow biopsy should be performed no more than 30 days <u>prior</u> to the initiation of conditioning.**

[8] GVHD assessments are performed weekly from Day +7 through Day +63 post-transplant, and then at Days +100, +180, +270, and +365 post-transplant. GVHD assessment on days 7 and 28 must be done within 24 hours <u>prior</u> to NK infusion. The GVHD assessment will include a review of all abnormalities experienced during the entire assessment period and the highest stage for each abnormality during the assessment period will be recorded on the GVHD eCRF. The Chronic GVHD Provider Survey will record GVHD symptoms present in the last week and be completed by a clinician on the day of the assessment.

[9] AEs and SAEs will be reported from Day -2 (1st dose of KDS-1001) through100 days post transplant. All SAEs must be reported to the IND Office (refer to Section 9).

[10] Chimerism may be evaluated in whole blood or blood cell fractions if sufficient cells are available, including CD3 and CD33 or CD15 fraction, according to institutional practice. The actual measurement dates may be within +/- 7 days of the recommended time points. Remaining DNA sample after chimerism studies may be used for correlative studies

[11] Day 100 DLCO if clinically indicated.

4.1 Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care.
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7. The home physician will be requested to report to the MDACC physician investigator all life-threatening events within 24 hours of documented occurrence.
8. Patients will be evaluated either in person or remotely via telemedicine.

5.0 Treatment Plan

In this study 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+).

The NK product on this trial will be manufactured by Kiadis Pharma per their OTS protocol. T cell spec corresponds to max 1% of the target formulated NK cells. The T-cell dose of each infusion should be ≤ 5.0×10^5 viable $CD3^+$ cells/kg over approximately 30 minutes.

Treatment plan by day

D-8 Admit/ Hydration.

D-7 to D-6 Melphalan Administration: Patients < age 60 receive melphalan 140 mg/m2 IV split into two doses (70 mg/m2 IV each day).
Patients age 60-70 receive melphalan 100 mg/m2 IV (infused per package insert) split into two doses (50 mg/m2 IV each day).

D-7 to D-4 Fludarabine Administration. Fludarabine will be administered at the dose of 40 mg/m2 IV daily for four doses on days -7 to -4. Patients weighing within 20% above their ideal body weight will be dosed according to actual body weight. Patients weighing more than 20% above their ideal body weight will be dosed according to the adjusted body weight. Formula to calculate adjusted body weight: Adjusted BW (Kg) = IBW + 0.5 (Actual body weight-IBW).

D-3 TBI 200 cGy on D-3.

D-2 NK cell (KDS-1001) administration
KDS-1001 is an NK cell suspension for intravenous administration and will be supplied frozen. The patient will receive $3x10^7$ (+/- 20%) NK cells/kg IV on D-2.

Prior to administration of KDS-1001
30 minutes prior to KDS-1001 administration, patients may be pre-medicated with diphenhydramine hydrochloride 25 mg IV or PO, acetaminophen 650 mg PO, or the preferred pre-medications, according to institutional policy or investigator discretion.

- Patients should have vital signs q15 minutes throughout the administration, monitored q1 hour for 4 hours after the completion of administration.
- To be eligible to receive the first administration of KDS-1001, patients must meet the following requirements at the time of the administration or must be removed from study:
    - No systemic corticosteroids within 72 hours of KDS-1001 dosing (≥10mg/day prednisone or equivalent).
    - Steroids should be avoided for at least 7 days after the administration, unless clinically required.
    - No uncontrolled infection or fever greater than or equal to 38.5◦C (101.3 degrees F) within 24 hours.
- AE assessment will be performed at every visit.

Should the patient experience a reaction while study medication is being administered, the injection will be interrupted and the patient evaluated. The treating physician may administer acetaminophen and/or diphenhydramine per institutional standards or may consider stopping the injection.

D-1 Rest

D0 Donor Hematopoietic stem cell transplant Infusion of a non T-cell depleted graft (from bone marrow or peripheral blood).

D+3 and D+4 Post Transplant Cyclophosphamide Administration with Mesna:

Patients will receive a dose of Mesna 10 mg/kg IVPB just prior to the first dose of cyclophosphamide, that will be repeated every 4 hours for a total of ten (10) doses. Patients will also receive ondansetron (or a comparable anti-emetic) prior to each dose of Cyclophosphamide (Cy).

Patients will receive Cyclophosphamide at a dose of 50 mg/kg per dose. Patients will receive mesna and cyclophosphamide according to ideal body weight or actual weight, whichever is lower.

It is recommended to receive IV fluids at a rate of 1.5-2 ml/kg/hr starting 2 hours before each dose of Cy and continued for a total of 10 hours, then resuming the previous IV fluids.

D+5 GvHD prophylaxis with Tacrolimus and Mycophenolate Mofetil should be started per standard practice. Tacrolimus start 0.015 mg /kg (based on IBW (adjusted to a level 5-15 ng/mL) IV daily then continued PO for at least 6 months post transplant. The dose may be modified as clinically indicated. Mycophenolate mofetil (MMF) 15 mg/kg (max. 1000mg per dose, based on actual body weight) p.o. TID. It is recommended to discontinue MMF after day +35 and to start tapering tacrolimus at D+180, tapering off over at least 3 weeks. Immunosuppressive treatment can be modified as clinically indicated.

G-CSF and Supportive Care Antimicrobial prophylaxis as per standard practice.

D+7 and D+28 (with flexibility per table 1) Second and Third KDS-1001 administration (As on D-2).
NK cell administration: To be able to receive the subsequent KDS-1001 administration(s) patients must meet the following requirements:

1. No uncontrolled infection or fever >38.5 C within 24 hours
2. No active GVHD requiring systemic steroid treatment.
3. No systemic corticosteroids within 72 hours of KDS-1001 dosing (≥10mg/day prednisone or equivalent).
4. Steroids should be avoided for at least 7 days after the administration, unless clinically required.

30 minutes prior to KDS-1001 administration, patients may be premedicated with diphenhydramine 25 mg intravenous piggyback (IVPB) or PO, acetaminophen 650 mg PO, or the preferred pre-medications, according to institutional policy or investigator discretion.

Epinephrine and antihistamines should be available at the patient's bedside during the NK cell administration to help treat any allergic reaction that might occur.

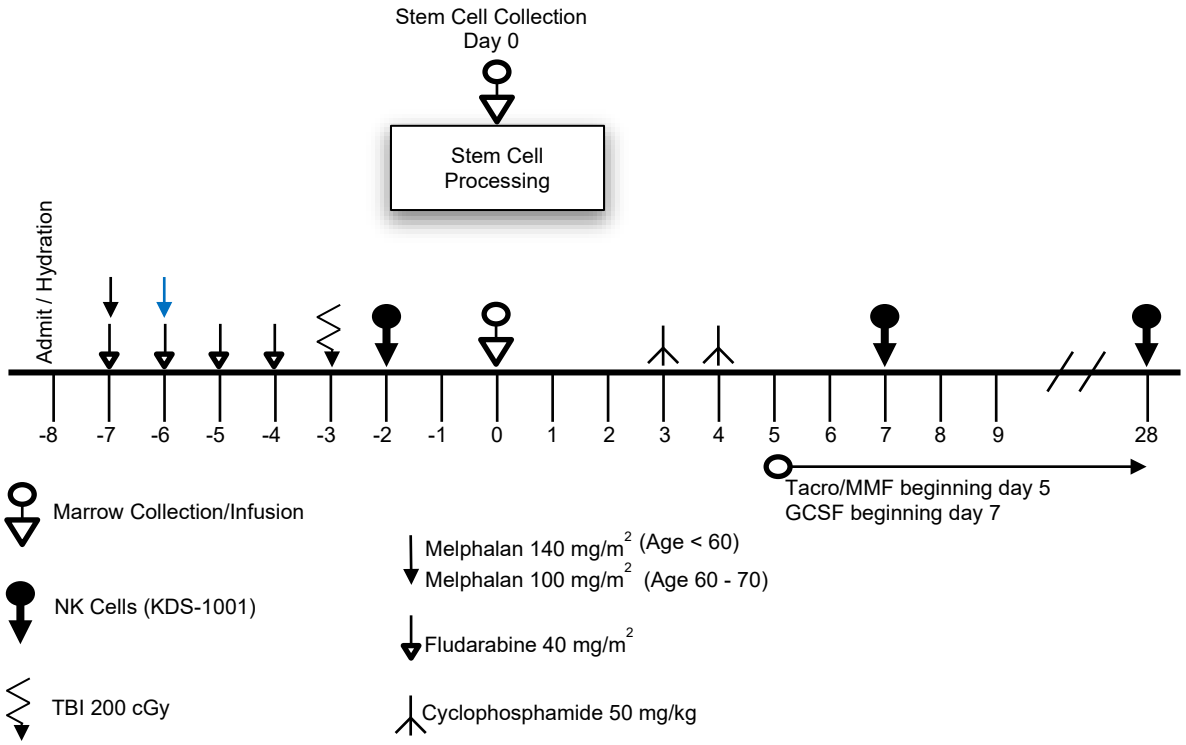
For day 28 infusion, patient must have recovered neutrophils> 1.0 x 10^9/liter.
On day +28 infusion, vital signs should be monitored q15 minutes throughout the administration and q1 hour x 1 after infusion.

If patients do not meet these criteria on the planned day 7 infusion, the cells can be given within the next week if the problem resolves; for the day 28 NK cell infusion, they may receive the NK cells within two weeks if the problem resolves and patients meet these criteria.

If possible, corticosteroids should be avoided within prior 72 hour period prior to NK cell administration (less than 0.5mg/kg prednisone or equivalent) and for 7 days after the administration. Corticosteroids may be administered if clinically necessary at the discretion of the attending physician.

D+7 Filgrastim or biosimilar filgrastim 5mcg/kg/day (rounded to the nearest vial) s.q. once a day daily until neutrophil recovery.

Antimicrobial prophylaxis will be employed according to the departmental standard practice. The recommended supportive care guidelines may be modified at the discretion of the patient's attending physician as clinically indicated.



6.0 Endpoints

The period of active treatment is from study entry to day +100 post transplant. After that time, patients are monitored for development of chronic GVHD, relapse and survival.

Primary endpoint
The primary endpoint is the composite adverse event Failure = graft failure, grade 3-4 GVHD, relapse or non-relapse death within 100 days post-transplant.

Secondary endpoints

i. All grade 1-5 adverse events during or within 24hours of KDS-1001 administration including CRS and infusion related toxicity will be tabulated (CTCAE v5.0)
ii. All grade 1-5 adverse events starting Day -2 (first KDS-1001 administration) through 100 days post transplant will be tabulated (CTCAE v5.0).
iii. Donor cell engraftment and graft failure will be assessed with donor/recipient chimerism studies at day+28 and day+100.
iv. Day+100, Day+180 and 1-year post-transplant:

a. Time to relapse or Death (Kaplan Meyer curves for DFS and OS)
b. Cumulative incidences for Relapse and NRM
c. Cumulative incidences for grade 2-4 and grade 3-4 acute GVHD, and chronic GVHD
d. GRFS

v. All grade 2 and higher infections will be described. Cumulative incidence of CMV reactivation, symptomatic BK hemorrhagic cystitis and Adenovirus infection at day+100 and day+180 will be described.
vi. Immune reconstitution of T and NK cells and function of NK cells post-transplant at day+28, day+100 and 1-year post-transplant

Definitions for endpoints

Active treatment administration is defined from the first day of treatment administration as outlined in the treatment plan through the NK administrations.
Active treatment period is defined from the first day of treatment administration through 30 days post the third NK administration.
Follow-up period is defined from 31 days post the third NK administration 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 and day+100 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.
Acute GVHD will be graded according to tables below. Time of onset of acute grades II-IV and III-IV GVHD will be recorded, as well as the maximum grade achieved.

Table 1: Staging of acute graft versus host disease

	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	< 500 mL diarrhea/day	501-1000 mL/day	1001–1500 mL/day	> 1500 mL/day	Severe abdominal pain & ileus
UGI		Severe nausea/vomiting			
Liver	Bilirubin ≤ 2 mg/dl	2.1-3 mg/dl	3.1-6mg/dl	6.1-15mg/dl	> 15 mg/dl

Table 2: Grading Index of Acute GVHD

Grade	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

Chronic GVHD will be reviewed as defined by the NIH 2014 Consensus(see Appendix 1) Conference Criteria to calculate the NIH global severity scores of mild, moderate and severe chronic GVHD.
CMV reactivation is defined as infection in a patient with previous evidence of CMV infection who has not had virus detected for an interval of at least 4 weeks during active surveillance.
Symptomatic BK hemorrhagic cystitis is defined as grade 1 by the presence of microscopic hematuria, grade 2 with patient-reported macroscopic hematuria, grade 3 with the passage of clots, grade 4 macroscopic hematuria with clots and an elevated creatinine secondary to obstruction as described by Bedi *et al*.

Disease Response as per CIBMTR criteria and documented in EPIC by the patient's treating physician.

A. For AML/MDS/CMML:
Complete remission (CR):
BM < 5% blasts (absence of blasts with Auer rods).
ANC > 1000/ul.
Platelet count >100 x $10e^9$/ul (independent of red cell transfusions).
Red blood cell transfusion independence.
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 $10e^9$/ul.
Absence of extramedullary disease.
No Response (NR) or Disease Progression/Relapse
BM > 5% leukemia blasts
Persistent presence of blasts in peripheral blood.
Presence of extramedullary disease.
Primary induction failure with response to therapy shown by adequate cytoreduction including <5% blasts or aplastic/hypoplastic marrow with no extramedullary disease and no blasts in peripheral blood detectable.

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.

Relapse of CML is defined as cytogenetic relapse, detection of t(9;22).

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.

7.0 Statistical Considerations

7.1 Preliminaries

This is a single-arm Phase II trial of 3rd party natural killer (NK) cells at a fixed dose of 3 x 10^7 +/- 20% cells/kg added to an allogeneic stem cell transplant for AML/MDS/CML. The primary endpoint is the composite adverse event Failure = [graft failure, grade 3-4 GVHD, relapse or non-relapse death within 100 days post-transplant]. The stopping rule for time-to-failure (defined as graft failure, gr 3-4 GHVD, relapse or non-relapse death) will be implemented per Section 7.3.

The secondary endpoint is T= time to relapse or death = RFS time.

7.2 Sample Size

The maximum sample size will be 24, and the anticipated accrual rate is 2 patients/month. This sample size will ensure that, for example, if p = Pr(T> 3 months) follows a non-informative beta(.65, .35) prior and 21/24 patients have T> 3 months, then the posterior of p will be beta(21.65, 3.35) with 95% credible interval .71 -- .97 for p.

7.3 Time-to-Failure Monitoring Rule

To avoid waiting 100 days (3 months) to evaluate each patient to perform safety monitoring, the design will be based on T with 3 months follow-up, applying the design of Thall et al[24]. The failure rate will be monitored as follows: Denote S = standard historical therapy, and E = the experimental NK cell therapy. Assume that T associated with S follows an exponential distribution with median mS and that T associated with the E follows an exponential distribution with median mE. Under a Bayesian model, both mS and mE are assumed to follow Inverse Gamma (a, b) priors, denoted IG(a, b). It will be assumed, based on historical experience, that Pr(T > 3 months) has mean .65, which corresponds to median(T) = 4.83 months under the assumption of exponentially distributed T. It is desired that, in this trial, Pr(T > 3 months) ≥ 0.85, which corresponds to a median(T) = 12.80 months or longer. For priors, we assume that mS ~ IG (13.73, 61.51), which has mean = 4.83 months and variance = 2.0 months, and that mE ~ IG (3, 9.66), which has the same mean = 4.83 months and the much larger variance = 23.33 months, reflecting little prior knowledge about E. Possibly right-censored values of T for patients treated with E in the trial will be monitored continuously throughout the trial.

Early Stopping Rule. Accrual to the trial will be terminated early if, at any time,
Pr(mE > mS + 100 days| data) < 0.05

The accrual rate is expected to be approximately 2 patients per month, with each patient's follow-up continued until all patients have been followed for 3 months from their date of first NK cell administration. This rule was constructed under the assumption that that true mE =

12.80 months or larger is acceptable, but smaller values are undesirable. The operating characteristics (OCs) of this time-to-failure stopping rule were computed using the program One-Arm TTE v 3.0.8 developed by the Department of Biostatistics at M.D. Anderson Cancer Center, available at the website:

https://biostatistics.mdanderson.org/SoftwareDownload/.

The OCs of the stopping rule, based on 1000 replications of the trial for each assumed true median failure time, are summarized in Table 2. These operating characteristics assume that trial monitoring occurs at the time of each new patient accrual.

Table 2. Operating characteristics of the time-to-failure stopping rule

True Median of T (months)	True Pr (T > 3 months)	Pr (Stop Early)	Mean Sample Size
3.48	0.55	0.96	9.1
4.83	0.65	0.70	13.9
7.23	0.75	0.33	18.9
12.80	0.85	0.10	22.1
40.54	0.95	0.02	23.7

If grade ≥ 3 CRS or Grade ≥ 3 infusion reactions occur, we will report this event to the IRB and hold the study for review. The protocol will not resume until approved to proceed by the IRB. The study will also be stopped if an excess rate of cytomegalovirus (CMV) viremia occurs ≥70% (4 or more of the first 5 patients or >70% of patients thereafter).

7.4 Data Analyses

The distributions of time to failure and RFS time will be estimated using the method of Kaplan and Meier[25]. Each of these distributions also will be estimated as functions of patient baseline covariates, including age, disease type, and whether the patient had active disease at transplant, by fitting a Bayesian survival time regression model[26,27], with the distribution chosen based on preliminary goodness-of-fit analyses.

Failure event times will be monitored continuously during the trial, using the Biostatistics Department Clinical Trial Conduct (CTC) website.
The stopping rule will be applied each time a new patient is accrued, or each time a patient has a "failure" event, to decide whether the trial should be stopped or not. The data for each patient at each time the rule is applied will consist of 2 statistics: (1) time from initiation of the patient's treatment to the event or last follow up time, (2) an indicator of whether the patient had a "failure" event at last follow up.
Each patient's (1) date of enrollment, (2) date of a failure event if it occurs, will be immediately entered into the CTC software, which will be set up for the trial on the CTC website prior to enrollment of the first patient. If a patient is followed for 100 days without a failure, then that patent's data will be considered complete for the purpose of applying the monitoring rule.

All secondary endpoints will be tabulated using mean, median, and range for numerical valued variables, and counts and percentages for binary or categorical variables. Kaplan-Meier plots will be used to estimate the distributions of all possibly right-censored time-to-event variables.
The Investigator is responsible for completing safety summary reports and submitting them to the IND Office Medical Affairs and Safety Group for review and approval. These should be submitted after the first 4 evaluable patients complete 100 days post transplant and every 4 evaluable patients thereafter. Subjects who are considered to be evaluable for efficacy have received three KDS-1001 infusions, undergone SCT, and completed 100 days post SCT assessment.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.0 Criteria for Removal from the Study

1. Disease progression requiring further treatment.
2. Prolonged cytopenia requiring treatment beyond GCSF.
3. Unexpected pattern of toxicity.
4. Patient withdrawal of the informed consent.
5. Patient is noncompliant with treatment schema.
6. After one year of treatment completion.

9.0 Reporting Requirements

Adverse event definition

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug (study medication), and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

An AE or suspected adverse reaction (AR) is considered "unexpected" if it is not listed in the Reference Safety Information (RSI) of the IB or is not listed at the specificity or severity that has been observed.

Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or other abnormal assessment findings constitute AEs or SAEs only if they induce clinical signs or symptoms, are considered clinically significant, require medical or surgical intervention, or leads to

study medication discontinuation, delay or interruption.

The severity of the AEs will be graded according to the Common Terminology Criteria v5.0 (CTCAE) from the start of the first NK cell administration up to 100 days from the last NK administration. Events not included in the CTCAE chart will be scored as follows:

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.
Grade 5: Death

Known adverse events
No clinical data have been reported yet with KDS-1001. From the clinical experience with other (expanded) NK cell preparations to date the overall conclusion is that NK cell infusions are safe and well tolerated, even in very high doses and repeated administration (refer to Table 3). AEs associated with infusion of allogeneic, expanded NK cells are the following:

Common (within 1-2 days of receiving drug)
- Flu-like symptoms, including fever, chills, cough, dyspnea, myalgia, arthralgia, fatigue, headache.
- Cryoprotectant (DMSO) associated adverse events, including unusual taste or odor, increased or decreased blood pressure, tachycardia, and headache.

Uncommon/rare (within 1-2 days of receiving drug)
- Acute infusion reaction, including fever, chills, cough, dyspnea, hypoxia, pulmonary edema, hypotension, tachycardia, angioedema, bronchospasm, rash, pruritis, myalgia, headache, hematuria, renal insufficiency.

The above common and uncommon AEs are anticipated to be ≤ Grade 3 events, occur in the first 24 hours after NK cell infusion, are responsive to supportive care, and resolve within 72 hours. In addition, in rare cases CRS and GVHD were reported.

- Cytokine release syndrome

CRS was reported in one of the studies in 2 of 16 patients receiving non-expanded IL 2-activated NK cells from haploidentical donors33. If symptoms of cytokine release syndrome are observed treatment should be initiated according to institutional standards. See Neelapu et al, Nature 2017;15:47.

- GVHD

In general, the role of NK cells in mediating GVHD has been the subject of much debate.

The contribution of NK cells in the development of GVHD remains elusive due to conflicting evidence emerging from a variety of different experimental approaches42,43. It is hypothesized that presumed sub-optimal timing of NK cell infusion with respect to timing of HSCT engraftment, and a more rapid T cell (CD3+ cell) engraftment observed in patients who developed GVHD may have contributed to the development of GVHD in certain studies with NK cells, while a number of other studies have promoted the notion that NK cells, in allogeneic adoptive transfer settings, help prevent GVHD by suppressing alloreactive T cells.

GVHD may also occur from contaminating T cells in the NK cell product. NK preparations with a T cell content of less than 1% were not associated with GVHD20. CD3+ lymphocytes present in the KDS-1001 product is limited by the release specifications for the final product. If grade 2 or greater acute GVHD occurs, it will be initially treated with corticosteroids (prednisone 2 mg/kg or equivalent). Additional immunosuppressive treatment will be given as clinically indicated. See Department GVHD treatment guidelines.

- CMV infection

CMV positive donors are selected for the manufacturing of KDS-1001 based on the observed correlation of higher NKG2C expression on NK cells sourced from these donors. The risk of the CMV virus passing from the donor to the recipient via the NK cell product, although very small, cannot by excluded[48,49]. Between 50 and 80% of people in the US have had a CMV infection before age 40-50. In persons with normal immune systems, CMV infection normally does not pose a risk. CMV monitoring and, if needed, treatment is recommended according to institutional guidelines.

Table 3. Overview of AEs Reported after Infusion of Allogeneic NK Cell Therapies

Common	Occasional	Rare

• Flu-like symptoms
  • Fever
  • Chills
  • Cough
  • Dyspnea
  • Myalgia
  • Arthralgia
  • Fatigue
  • Headache
• Cryoprotectant (DSMO) associated:
  • Unusual taste
  • Increased or decreased blood pressure
  • Tachycardia
  • Headache
	• Acute infusion reaction
	  • Fever
	  • Chills
	  • Cough
	  • Dyspnea
	  • Hypoxia
	  • Pulmonary edema
	  • Hypotension
	  • Tachycardia
	  • Angioedema
	  • Bronchospasm
	  • Rash
	  • Pruritus
	  • Myalgia
	  • Headache
	  • Hematuria
	  • Renal insufficiency
		• Cytokine release syndrome
		• Graft-versus-host disease (GVHD)

Serious Adverse Event (SAE) Reporting Requirements for M D Anderson

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 event
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 on Reporting Adverse Events for Drugs and Devices”.

Serious adverse events will be captured from Day -2 (first KDS-1001 administration) through 100 days post transplant, unless the participant withdraws consent.

Serious adverse events will be captured from the time of the first protocol-specific treatment until 100 days after the last KDS-1001 administration, 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.

All SAEs, expected or unexpected/ initial or follow up, must be reported to the

IND Office within 5 working days of knowledge of the event regardless of the attribution.

Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office within 24 hours of knowledge of the event

Additionally, any serious adverse events that occur after the 100 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.

OnCore will be utilized for safety reporting to the IND Office and MD Anderson IRB.
All events reported to the supporting company must also be reported to the IND Office.

Reporting to FDA:
Serious adverse events will be forwarded to FDA by the IND Sponsor 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.

Investigator Reporting to Kiadis:

Initial SAEs and/or subsequent follow-up reports will be reported to Kiadis on the MDACC Institution Adverse Event Report Form at the time it is submitted to MDACC IND Office. SAE reports should be for a single subject.

Email report to:
CL-CPV-Receipt@sanofi.com

Copy:
Dr. Klaudia Traudtner
Head of Safety and Pharmacovigilance, GPV Oncology
Email: Klaudia.Traudtner@sanofi.com

Periodic safety reporting:
WW-GPV-GlobalPeriodicReports@sanofi.com

Events not considered to be SAEs are hospitalizations that are expected, such as:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition;

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the studied indication and has not worsened since signing the informed consent;
- Hospitalization for a procedure that is planned (i.e., planned prior to starting of treatment on study) must be documented in the source document and the CRF.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

10.0 Adverse Events and Data Collection

For the purpose of this study, the investigational component of the treatment plan is [KDS-1001]. Therefore, serious and unexpected AEs occurring from Day -2 (first KDS-1001 administration) through 100 days post transplant, as defined below, will be reported according to MDACC policy and procedures below to BMTWeb The end of active treatment is the completion of the three NK cell administrations]. AEs or SAEs that are considered causally related to the KDS-1001 administration need to be reported throughout the entire study period. Pregnancy of a female patient or partner of a male patient should be followed until either termination of the pregnancy for whatever reason or birth.

Serious adverse events must be followed until clinical recovery and laboratory test have returned to values within normal range progression of the event has stabilized, or there has been acceptable resolution of the event. SAEs determined to be due to progression of the underlying disease should be recorded but not be subject to expedited reporting. All SAEs related to the disease but unrelated to the study medication administration should be reported annually to the FDA and IRB.

10.1 Common Terminology Criteria Adverse Events (CTCAE)

A descriptive terminology developed by the National Cancer Institute (NCI) for use in reporting adverse events. The CTCAE includes a grading (severity) scale for each adverse event term. A copy of CTCAE version 5.0 can be downloaded from the CTEP website. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Grade – Severity of the adverse event. Grades were developed using the following guidelines:

Grade 0 – No adverse event or lab values within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

Abnormal laboratory values not included in the CTCAE guidelines will be defined per protocol.

The relationship/attribution of each AE to the investigational product will be assessed by the investigator after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant medical history, pattern of the AE, temporal relationship to the study medication and dechallenge or rechallenge according to the following guidelines:

Possibly, Probably, or Definitely Related: there is a reasonable possibility and/or evidence that the study drug caused the event if One or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of investigational product;
- The event could not be reasonably attributed to the known characteristics of the patients clinical state, environment, or toxic factors or other modes of therapy, administered to the patient;
- The event follows a known pattern of response to investigational product;
- The event disappears or decreases on cessation or reduction in dose of the investigational product. In some situations, an AE will not disappear or decrease in intensity upon discontinuation of the investigational product despite other clear indications of relatedness.

Unlikely, or Not Related: There is no reasonable possibility that the investigational product caused the event if one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug;
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment, or toxic factor or other modes of therapy administered to the patient;
- The event does not follow a known pattern of response to investigational product;
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the investigational product is re-administered.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

10.2 Time for AE Collection

Adverse events will be collected Day -2 (first KDS-1001 administration) through 100 days post transplant.

AEs or SAEs that are considered causally related to the KDS-1001 administration need to be reported whenever they occur. Pregnancy of a female patient or partner of a male patient should be followed until either termination of the pregnancy for whatever reason or birth.

10.3 AE reporting

The Investigator or physician designee is responsible for verifying and providing source documentation for all AEs and assigning attribution for each event on all subjects enrolled in this study.

10.4 Data collection

Collection of AEs will reflect the onset and resolution date and maximum grade. Indeterminate events should be labeled as such and followed until resolution. If a patient is taken off the study while an event is still ongoing, the event 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.

Patients will be registered in MD Anderson's Clinical Trial Management System, OnCore.

Adverse events and protocol specific data will be entered into BMTWeb. BMTWeb will be

used as the electronic case report form for this protocol.
Events not to be considered AEs in this study are those related to the original disease or expected in the post-allogeneic transplant period.

Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of GPT, GOT, LDH and alkaline phosphatase will not be monitored.

10.5 Concomitant medications

Patients treated in this study will require supportive care treatment (concomitant medications). These medications are considered standard of care and have no scientific contribution to the protocol; therefore no data will be captured on various medications needed or their side effects (but side effects of concomitant medications should be considered when making a causality assessment of any AE or SAE during the study at the discretion of the P.I.). All antiviral therapy will be captured in the medical record.

11.0 Regulatory considerations

11.1 Institutional Review Board

This protocol and the proposed ICF must be reviewed and approved by the FDA and IRB prior to the start of the study. No modifications to the protocol will be made without the approval of the sponsor (MDACC IND Office) and the IRB prior to implementation.

It is the investigator's obligation to maintain a regulatory file, and to make this available for review by sponsor representatives as part of the study monitoring process.

During the study, the investigator shall make timely and accurate reports to the FDA and IRB on the progress of the trial, at intervals not exceeding 1 year.

11.2 Study Conduct

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH Guidelines for GCP and applicable regulatory requirements.

The investigator will ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and study-related duties.

11.3 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all data provided to the sponsor or designee, study

reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers shall be limited to the site and the study physician and shall not be disclosed to the sponsor or designee.

11.4 Written Informed Consent

The investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and entry into the study. The investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated ICF must be obtained before conducting any study procedures. A copy of the signed ICF must be given to the subject.

12.0 Background Drug Information

12.1 All drugs listed below are available commercially. Refer to the FDA approved package inserts for complete product information, pharmacology, including how supplied, storage and stability, special precautions, reconstitution, and administration instructions. Dose rounding/standardization is permitted as per institutional policy for all commercially available chemotherapy and supportive care agents.

12.1.1 Fludarabine (Fludara™)

Fludarabine is a fluorinated nucleoside analog.

Mechanism of Action: After phosphorylation to fluoro-ara-ATP the drug appears to incorporate into DNA and inhibit DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis.

Known Side Effects: pancytopenia, immunosuppression, autoimmune hemolytic anemia have (rarely) been reported, and recurred when patients were retreated with the drug. GI toxicity: Nausea, vomiting, anorexia, weakness. CNS toxicity: agitation, visual disturbances, confusion, coma, peripheral neuropathies. With high dose use confusion, blindness, coma and death have been reported. Please refer to the package insert for a complete listing of all toxicities.

12.1.2 Melphalan

Melphalan is an alkylating agent, which is a derivative of mechlorethamine.

Mechanism of Action: Melphalan inhibits DNA and RNA synthesis via formation of

carbonium ions; cross-links strands of DNA. Melphalan acts on both resting and rapidly dividing tumor cells.

Known Side Effects: Dose limiting toxicity is expected to be hematological when used without stem cell support. Other toxicities seen frequently following melphalan in preparative regimens for bone marrow transplantation include: peripheral edema, fatigue, dizziness, hypokealemia, hypophosphatemia, diarrhea, nausea, vomiting, constipation, mucositis, stomatitis, dyspepsia, fever, renal failure, amenorrhea, hematochezia, hypersensitivity reaction, SIADH, veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS). Please refer to the package insert for a complete listing of all toxicities.

12.1.3 Cyclophosphamide (Cytoxan™)

Cyclophosphamide is an alkylating agent.

Mechanism of Action: Cyclophosphamide prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is cell cycle phase non-specific. Cyclophosphamide also possesses potent immunosuppressive properties. It is a pro-drug metabolized by the liver to active metabolites.

Known Side Effects: Hematologic: Leukopenia, anemia, alopecia. GI: Nausea, vomiting, increased AST, ALT, mucositis, and diarrhea. Neurologic: Headache, dizziness. Cardiovascular: Cardiomyopathy, non-specific ST changes on EKG. Please refer to the package insert for a complete listing of all toxicities.

12.1.4 Mesna (sodium -2-mercapto ethane sulphonate, Mesnex™)

Mesna is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxazophosphorines (cyclophosphamide and ifosfamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy.

Mechanism of Action: Mesna binds with acrolein, the urotoxic metabolite produced by the oxazophosphorines, to produce a non-toxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxazophosphorines.

Known Side Effects: At the doses used for uroprotection, mesna is virtually non-toxic. However, adverse effects which may be attributable to mesna include nausea and vomiting, diarrhea, abdominal pain, altered taste, rash, urticaria, headache, joint or limb pain, hypotension and fatigue. Please refer to the package insert for a complete listing of all toxicities.

12.5 Adoptive NK Cell Therapy

NK Cells Expanded with mbIL-21 and 4-1BBL (KDS-1001)
Ex-vivo expansion of NK cells using a modified K562 cell line that expresses mbIL-21 and 4-1BB ligand (FC21-NK) allowed infusion of large number of NK cells to patients12. FC21-NK continue to be used worldwide in clinical trials. Adoptive transfer of these donor derived

expanded NK cells was safe up to doses of 1 x 10^8 NK cells/kg and resulted in clinical relevant response rates such as reducing tumor burden and relapse rates (Section 5.3). Although the feeder cell system enabled the robust generation of large numbers of highly active NK cells to perform clinical trials, the expansion process was refined through the development of PM21 membrane particles, which can as effectively stimulate expansion of NK cells13. PM21 particles are formed from the plasma membranes of K562.mbIL21.41bbl (CSTX002) feeder cells.

KDS-1001 comprises allogeneic donor NK cells which have been expanded ex vivo using PM21 membrane particles. The use of PM21 particles circumvents the direct use of feeder cells. Similar expansion and pharmacological activity of expanded NK cells using feeder cells or PM21 particles has been demonstrated in in vitro and in vivo nonclinical studies (Section 4.1). Therefore, KDS-1001, expanded using the PM21 particles, is expected to have a similar clinical activity and safety profile as the mbIL-21 and 4-1BBL feeder cells expanded NK cells used in several oncology indications.

Use of PM21 particle expanded haploidentical NK cells (K-NK002), produced using the same manufacturing process, is cleared by the FDA and is currently being investigated in an ongoing clinical trial (NK-REALM, NCT04395092) as adjunctive treatment for patients with high risk myeloid malignancies undergoing a haploidentical hematopoietic stem cell transplantation (HSCT). In that study the NK cells are from the same donor as stem cells for the transplant. Kiadis Pharma is developing KDS-1001 as an off–the-shelf drug product from material from allogenic donor for immediate availability to the patient. Off the shelf Kiadis NK cells are cleared by the FDA for use in patients with solid tumors and in the infectious disease area.

In conclusion, NK cells expanded using the mbIL-21 and 4-1BBL are safe and clinically effective as a cancer therapy. The Kiadis off-the-shelf production process developed for KDS-1001 allows to make NK-cell therapy products rapidly available for a broad patient population across a potentially wide range of oncology indications.

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Appendix 1.

Chronic GVHD organ scoring from the 2014 NIH consensus as defined per Jagasia et al, 2015

Mild chronic GVHD

1 or 2 organs involved with no more than score 1 plus

Lung score 0

Moderate chronic GVHD

3 or more organs involved with no more than score 1
OR

At least 1 organ (not lung) with a score of 2
OR

Lung score 1

Severe chronic GVHD

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

Key points:
In skin: higher of the two scores to be used for calculating global severity.

In lung: FEV1 is used instead of clinical score for calculating global severity.

If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.

If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Figure 1. Organ Scoring of Chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	ϒ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	ϒ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	ϒ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	ϒ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† ☐ **SCORE % BSA** *GVHD features to be scored by BSA:* **Check all that apply:** ϒ Maculopapular rash/erythema ϒ Lichen planus-like features ϒ Sclerotic features ϒ Papulosquamous lesions or ichthyosis ϒ Keratosis pilaris-like GVHD	ϒ No BSA involved	ϒ 1-18% BSA	ϒ 19-50% BSA	ϒ >50% BSA
SKIN FEATURES SCORE:	ϒ No sclerotic features		ϒ **S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ϒ Deep sclerotic features ϒ "Hidebound" (unable to pinch) ϒ Impaired mobility ϒ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ϒ Hyperpigmentation ϒ Hypopigmentation ϒ Poikiloderma ϒ Severe or generalized pruritus ϒ Hair involvement ϒ Nail involvement ϒ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ϒ **Yes** ϒ **No**	ϒ No symptoms	ϒ Mild symptoms **with** disease signs but not limiting oral intake significantly	ϒ Moderate symptoms with disease signs **with** partial limitation of oral intake	ϒ Severe symptoms with disease signs on examination **with** major limitation of oral intake
ϒ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Figure 1. Organ Scoring of Chronic GVHD (continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ϒ **Yes** ϒ **No** ϒ **Not examined**	ϒ No symptoms	ϒ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	ϒ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	ϒ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
ϒ *Abnormality present but explained entirely by non-GVHD documented cause*				
GI Tract ***Check all that apply:*** ϒ Esophageal web/ proximal stricture or ring ϒ Dysphagia ϒ Anorexia ϒ Nausea ϒ Vomiting ϒ Diarrhea ϒ Weight loss ≥5%*	ϒ No symptoms	ϒ Symptoms without significant weight loss* (<5%)	ϒ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	ϒ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
ϒ *Abnormality present but explained entirely by non-GVHD documented cause*				
LIVER	ϒ Normal total bilirubin and ALT or AP < 3 x ULN	ϒ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	ϒ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	ϒ Elevated total bilirubin > 3 mg/dL
ϒ *Abnormality present but explained entirely by non-GVHD documented cause*				
LUNGS**				
Symptom score:	ϒ No symptoms	ϒ Mild symptoms (shortness of breath after climbing one flight of steps)	ϒ Moderate symptoms (shortness of breath after walking on flat ground)	ϒ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	ϒ FEV1≥80%	ϒ FEV1 60-79%	ϒ FEV1 40-59%	ϒ FEV1 ≤39%
Pulmonary function tests ϒ Not performed ϒ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Figure 1. Organ scoring of chronic GVHD (continued)

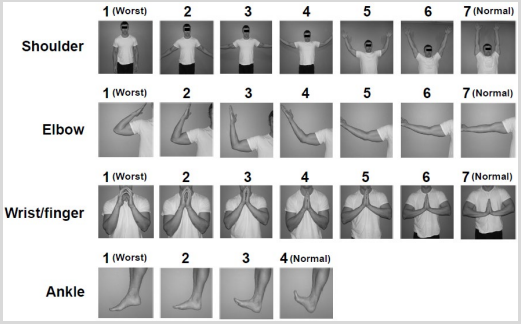
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	ϒ No symptoms	ϒ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	ϒ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	ϒ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
ϒ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ϒ Not examined *Currently sexually active* ϒ Yes ϒ No	ϒ No signs	ϒ Mild signs‡ and females with or without discomfort on exam	ϒ Moderate signs‡ and may have symptoms with discomfort on exam	ϒ Severe signs‡ with or without symptoms
ϒ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

ϒ Ascites (serositis)___	ϒ Myasthenia Gravis___	
ϒ Pericardial Effusion___	ϒ Peripheral Neuropathy___	ϒ Eosinophilia > 500/µl___
ϒ Pleural Effusion(s)___	ϒ Polymyositis___	ϒ Platelets <100,000/µl ___
ϒ Nephrotic syndrome___	ϒ Weight loss>5%* without GI symptoms ___	ϒ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑**No GVHD** ❑**Mild** ❑**Moderate** ❑**Severe**

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should

be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.
Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).
‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

Name:_____ Date of birth: _____Assessment date: _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GENITAL TRACT ***Check*:** ☐ Male ☐ Female	☐ No signs	☐ Mild signs and females may have symptoms* WITH discomfort on exam	☐ Moderate signs and may have symptoms* with discomfort on exam	☐ Severe signs with or without symptoms *

<u>Currently sexually active</u>: ☐ Yes ☐ No	
<u>Check all signs that apply</u>:	☐ Erosions
☐ Lichen planus-like features	☐ Fissures
☐ Lichen sclerosis-like features	☐ Ulcers
☐ Vaginal scarring (female)	☐ Phimosis (male)
☐ Clitoral/labial agglutination (female)	☐ Urethral meatus scarring/ stenosis (male)
☐ Labial resorption (female)	
☐ *Abnormality present but <u>NOT</u> thought to represent GVHD (specify* ☐ *Abnormality thought to represent GVHD <u>PLUS</u> other causes(specify cause):* _____	

**Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection*.

If a gynecologist is unavailable, external examination may be performed to determine "discomfort on exam" as follows:
a)Spread the labia majora to inspect the vulva for the above signs. Touch the vestibular gland openings (Skene's and Bartholin's), labia minora and majora gently with a qtip. Vulvar pain elicited by the gentle touch of a qtip is classified as discomfort on examination. Palpate the vaginal walls with a single digit to detect bands, shortening, narrowing or other signs of vaginal scarring.
b)If the woman is sexually active, determine whether qtip palpation or gentle palpation of scarred ridges elicits pain similar to that which the woman experiences during intercourse.

Female genitalia: Severity of signs:
1) Mild (any of the following); erythema on vulvar mucosal surfaces, vulvar lichen-planus or vulvar lichen-sclerosis.
2) Moderate (any of the following); erosive inflammatory changes of the vulvar mucosa, fissures in vulvar folds
3) Severe (any of the following); labial fusion, clitoral hood agglutination, fibrinous vaginal adhesions, circumferential fibrous vaginal banding, vaginal shortening, synechia, dense sclerotic changes, and complete vaginal stenosis.

Male genitalia: Diagnostic features include lichen planus-like or lichen sclerosis-like features and phymosis or urethral scarring or stenosis. Severity of signs:
1) Mild: lichen planus-like feature;
2) Moderate: lichen sclerosus-like feature or moderate erythema;
3) Severe: phimosis or urethral/meatal scarring.

Biopsy obtained: ☐ **Yes** ☐ **No** **Site biopsied:_____GVHD confirmed by**

histology: ☐ **Yes** ☐ **No**

Change from previous evaluation: ☐ **No prior or current GVHD** ☐ **Improved** ☐ **Stable** ☐ **Worse** ☐ **N/A (baseline)**

Completed by (print name):_____

Date form completed: _____

Appendix 2.

2017 ELN risk stratification by genetics

Risk Category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22; *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23.3;q34.1)/DEK::NUP214
	t(v;11q23.3)/KMT2A-rearranged#
	t(9;22)(q34.1;q11.2)/BCR::ABL1
	t(8;16)(p11.2;p13.3)/KAT6A::CREBBP
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1)
	t(3q26.2;v)/MECOM(EVI1)-rearranged
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,** monosomal karyotype††
	Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡
	Mutated TP53a

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.

† Low, low allelic ration (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3-ITD* allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3-ITD"* divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3-ITD* low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT. [57—59, 77]

‡ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§ Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8:21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1.

‖ Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]