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# Phase I/II clinical trial of Daratumumab in patients with relapsed acute myeloid leukemia post-allogeneic hematopoietic stem cell transplant.

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**Drug and Funding Supporter**
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**IND Sponsor:**
The Ohio State University

# 1 Table of Contents

# 2 PROTOCOL SYNOPSIS

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| Title | Phase I/II clinical trial of Daratumumab in patients with relapsed acute myeloid leukemia post-allogeneic hematopoietic stem cell transplant. |
| Protocol Short Title | Daratumumab in post-transplant relapse |
| Name of Drug | Daratumumab |
| Study Rationale | 1. IFN-γ promotes graft-versus-leukemia effects without directly interacting with leukemia cells in mice after allogeneic hematopoietic cell transplantation.<br>2. Endogenous IFN-gamma levels are elevated in post-transplant patients post-conditioning, infections, GVHD, and during hematopoietic regeneration.<br>3. We hypothesize that (i) IFN-gamma levels will be higher in post-transplant patients than healthy donors (ii) combination of Daratumumab and endogenous IFN-gamma will mediate antileukemic efficacy post-transplant (iii) the combination of Dara and donor lymphocytes will provide potent effectors, recruit effectors to marrow and mediate GVL. |
| Treatment Duration | 8 weeks; Daratumumab may be continued beyond 8 weeks if clinical benefit is observed up to 12 months. |
| Dosing Schedule | Weekly Dara for 8 doses |
| Route | Intravenous |
| Age range | ≥ 18 years |
| Study Duration | 10 months to 3.5 years for phase I; 24 months for phase II. |
| Sample size | 8-40 patients for Phase I; 25 patients for phase II |
| Inclusion Criteria | 1. Patients ≥ 18 years<br>2. AML relapse following Allo-HSCT (Morphological relapse, or MRD positive verified by flow cytometry, cytogenetics, and molecular mutations) |

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| | 3. For patients in Dose level 1 (Daratumumab only), relapsed refractory AML patients who have previously not received an allogeneic HCT are eligible.<br>4. Patients with R/R AML must not be candidates for available therapies known to be effective for treatment of their AML.<br>5. MDS transformed to AML following Allo-HCT<br>6. Patients who received a 10/10 HLA-matched allogeneic HCT either from sibling donors or unrelated donors or atleast a 5/10 haploidentical transplant for dose levels needing DLI<br>7. Engraftment must have occurred as defined by platelet (PLT) count > 20,000/μL and ANC ≥ 0.5<br>8. ECOG performance status < 3<br>9. Creatinine clearance > 40 ml/min (Calculated or measured)<br>10. Aspartate aminotransferase (AST) < 3 x upper limit of normal (ULN), alanine aminotransferase (ALT) < 3 x ULN, and total bilirubin < 1.5 x ULN<br>11. Off calcineurin inhibitors for at least 2 weeks<br>12. Prednisone dose ≤ 20 mg/day<br>13. Patients with proliferative disease can be cytoreduced with cytotoxic chemotherapy at investigator's discretion, but there should be at least a 14 day window between start of cytoreductive therapy and start of Daratumumab<br>14. Blast count <20K/day (hydrea use is allowed)<br>15. Female patients of childbearing potential who are sexually active must be willing to use an effective barrier method of birth control to avoid pregnancy during the study and for a minimum of 3 months after stopping study treatment<br>16. Male patients must agree to not donate sperm and if sexually active with partners of childbearing potential must be willing to use an effective barrier |

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| | method of birth control to avoid pregnancy during the study and for a minimum of 3 months after stopping study treatment |
| Exclusion Criteria | 1. No demonstrable evidence of donor chimerism (< 55% donor CD3 or CD33 chimerism)<br>2. Patients with a molecular mutation without chromosomal abnormalities or declining chimerisms (MRD status must be verified by surface marker and mutational analyses)<br>3. Active graft-versus-host disease (GVHD) grades I-IV; prior acute GVHD could have occurred but resolved at time of initiation of Daratumumab<br>4. Extensive chronic GVHD requiring ongoing immunosuppression with calcineurin inhibitors or more than 20 mg of prednisone<br>5. Patients with FLT3+ AML or blast crisis CML who have not yet received post-transplant TKI therapy<br>6. Active CNS or testicular disease<br>7. Subject is: seropositive for human immunodeficiency virus (HIV); seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.; seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy). |

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| | 8. Patients must not have chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) < 50% of predicted normal. FEV1 is required for patients suspected of having chronic obstructive pulmonary disease and are not eligible if FEV1 is < 50% of predicted normal.<br>9. Patients must not have moderate or severe persistent asthma within the past 2 years and must not have currently uncontrolled asthma of any classification.<br>10. History of grade IV anaphylactic reaction to monoclonal antibody therapy<br>11. Active autoimmune disease prior to transplant<br>12. Pregnancy<br>13. Female patients of childbearing potential who are sexually active and unwilling to use an effective barrier method of birth control to avoid pregnancy during the study and for a minimum of 3 months after study treatment<br>14. Male patients who wish to donate sperm or with partners of childbearing potential who are sexually active and unwilling to use an effective barrier method of birth control to avoid pregnancy during the study and for a minimum of 3 months after study treatment<br>15. Concurrent use of any other investigational drugs |
| Study Design | 1. Phase I study (3+3 study design) with the following dose levels:<br>For related sibling donors:<br>a. Dose level 1: Dara 16mg/kg<br>b. Dose level 2: Dara 16mg/kg + DLI at weeks 3-5: 1x10e6 CD3/kg<br>c. Dose level 3: Dara 16mg/kg + DLI at weeks 3-5: 1x10e7 CD3/kg<br>For unrelated donors: |

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| | d. Dose level 1: Dara 16mg/kg<br>e. Dose level 2: Dara 16mg/kg + DLI at weeks 3-5: 1x10e5 CD3/kg<br>f. Dose level 3: Dara 16mg/kg + DLI at weeks 3-5: 1x10e6 CD3/kg<br><br>For haploidentical donors:<br>g. Dose level 1: Dara 16mg/kg<br>h. Dose level 2: Dara 16mg/kg + DLI at weeks 3-5: 1x10e4 CD3/kg<br>i. Dose level 3: Dara 16mg/kg + DLI at weeks 3-5: 1x10e5 CD3/kg<br>2. Phase II study with maximal tolerated dose as established for both related and unrelated donors. The MTD for the DLI may be different for related and unrelated donors. |
| Study logistics | 1. Identify patient with suspected relapse<br>2. Trial discussed, consent obtained and bone marrow performed<br>3. If MRD positive or morphologic relapse, stop immunosuppression within a week of biopsy results<br>4. If no evidence of GVHD in 2 weeks after stopping immunosuppression, start Daratumumab.<br>5. Daratumumab may be given as outpatient or inpatient depending on treating physician discretion.<br>6. Patient will be seen prior to every Daratumumab dose and assessment for GVHD will be done<br>7. Plan bone marrow biopsy after doses 3 and before dose 4.<br>8. Administer DLI between weeks 3-5.<br>9. Resume weekly Dara weeks 6-8 |

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| | 10. Bone marrow biopsy after week 8 |
| Study Objectives – Phase I | **Primary Objectives:**<br>1. **Phase I:**<br>To determine the maximum tolerated dose (MTD) of Daratumumab and escalating doses of donor lymphocyte infusions (DLI) in post-HCT patients with relapsed AML and MDS transformed to AML.<br>2. **Phase II:**<br>To evaluate overall response rate to Daratumumab and DLI by week 8 in patients with post-HCT relapsed AML and MDS<br>**Secondary Objectives:**<br>1. To assess overall response rates in MRD positive patients and in patients with overt morphological relapse<br>2. To assess MRD conversion rates from MRD positive to MRD negative.<br>3. To determine the post-relapse 6-month OS rates of patients with relapsed AML and MDS following allo-HSCT who are treated with Daratumumab<br>4. To determine the rates of GVHD (both grades II-IV and III-IV) and autoimmune side effects of Daratumumab by 3 months.<br>5. To determine the post-relapse 6-month PFS rates of patients with relapsed AML and MDS following allo-HSCT who are treated with Daratumumab |
| Safety Assessment | Physical examination, electrocardiogram (ECG), clinical laboratory tests (hematology, blood chemistries, urinalysis, prothrombin time [PT], activated partial thromboplastin time [APTT]), anti-drug antibody (ADA), cytokine/inflammatory factor levels, vital signs, and adverse event/toxicity assessment. |
| Efficacy Assessment | Standard response assessment as defined for AML, duration of response, and overall survival/PFS. |

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| DLT definition | • Acute GVHD ≥ Grade 3<br>• Any non-hematologic toxicity ≥ Grade 3 related to Daratumumab<br>• Hematologic toxicity: grade 4 toxicity not related to the underlying disease and not responding to growth factor or transfusion within 7 days<br>• Grade 3 or higher non-neurologic immune-related adverse events (e.g. diarrhea, pruritus, rash) that responds to corticosteroids and improve to grade 1 or less within 4 weeks will NOT count as DLTs. Optional biopsy of affected organs will be encouraged to help determine whether the immune-related condition is due to GVHD |
| Enrollment schedule | Dose level 1: Weekly Dara for eight doses; if no infusional toxicity observed or GVHD observed, proceed to next dose level. 3 patients at a time can be enrolled in one dose level.<br>If no GVHD is observed after at least 2 weeks after DLI, enrollment will proceed to next dose level. |
| Definitions for safety-evaluability | Received at least one dose of Daratumumab |
| Definition for DLT evaluability | All patients are evaluable for DLT except patients who are unable to receive 3 doses of daratumumab in dose level 1, or 3 doses of daratumumab and DLT for dose levels 2 and 3 due to progression of AML.<br>DLT observation period will be from the first dose of daratumumab till 7 days post 3rd dose of daratumumab (for dose level 1) and from the first dose of daratumumab till at least 4 weeks post DLI (for dose level 2 and 3) |
| Definitions for efficacy evaluability: | All eligible patients who receive at least one dose of Daratumumab, do not withdraw consent, and are evaluated for response at week 8. |
| Dose-limiting toxicity: | Grade 3 or 4 GVHD |
| Special situations | 1. If patients attain response before DLI, there will be three options at the discretion of treating physician :<br>a. Proceed with DLI |

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| | b. Continue Daratumumab maintenance( If Daratumumab is given as maintenance, a schedule of 16mg/kg every 2 weeks for 16 (8 doses) weeks and then monthly for 6 months will be administered)<br>c. Proceed with second transplant.<br>2. If patients develop steroid-responsive GVHD and remission before DLI, there will be two options at the discretion of treating physician :<br>a. Continue Daratumumab maintenance (If Daratumumab is given as maintenance, a schedule of 16mg/kg every 2 weeks for 16 weeks (8 doses) and then monthly for 6 months will be administered)<br>b. Proceed with second transplant. |

# 3 KEY ROLES

Principal Investigator Dr. Sumithira Vasu MBBS

Statistician: Qiuhong Zhao MS.

# 4 INTRODUCTION

## 4.1 AML RELAPSE POST-TRANSPLANT

Acute myeloid leukemia (AML) is a molecularly heterogeneous disease with significant genetic complexity[1]. Allogeneic hematopoietic cell transplantation (Allo-HCT) has curative potential and most patients with intermediate or adverse risk molecular and cytogenetic subtypes will proceed to allogeneic HCT in first complete remission[2]. With increasing availability of donor sources and reduced-intensity conditioning, number of transplants is expected to increase. However, AML relapse incidence post Allo-HCT varies between 18-47% based on the conditioning regimen[3,4]. Relapse after Allo-HCT has a dismal prognosis, with a median post-relapse overall survival (OS) of 3-6 months[5,6]. According to historical cohorts, if not transplanted for a second time, such patients have a 6-month median OS of only about 10%. For example, chemotherapy and donor lymphocyte infusion provided discouraging post-relapse median OS of 51 and 84 days, respectively in a large recent study[5]. Although second Allo-HSCT may offer durable remissions[7] , only a small number of patients after relapse are eligible to receive a second transplant. In a recent CIBMTR analysis of 1788 patients relapsing after allogeneic HSCT, 3-year overall survival was 4% for patients relapsing within 1-6 months after an allograft and 12% for patients who relapsed in the 6-24 months after an allograft[8]. Currently, there is no standard or satisfactory treatment available for this group of patients. We propose here a Phase I/II study to determine the activity and safety of Daratumumab in patients post Allo-HCT with relapsed AML and myelodysplastic syndrome (MDS) transformed to AML.

## 4.2 ROLE OF DLI

Recent studies have shown T-cell exhaustion in post-transplant relapses and that it can be reversed during effective human antileukemic responses to donor lymphocyte infusion (DLI)[9]. There is increasing evidence that T cell infiltration at site of malignancy is critical to disease control. In a group of chronic myeloid leukemia patients who traditionally have the highest responses to DLI( about 85%), Bachireddy et al found that baseline T cell content in marrow and subsequent increase in T cell content following DLI were higher in responders versus non-responders. Recent guidelines note recommended doses of DLI for related and unrelated donors[10]. In the halo setting with post-transplant cyclophosphamide[11], Donor lymphocyte infusion with doses up to 1x10e6/kg were noted to have remission rates of up to 30% in patients with AML.

## 4.3 PRECLINICAL DATA REGARDING DARATUMUMAB

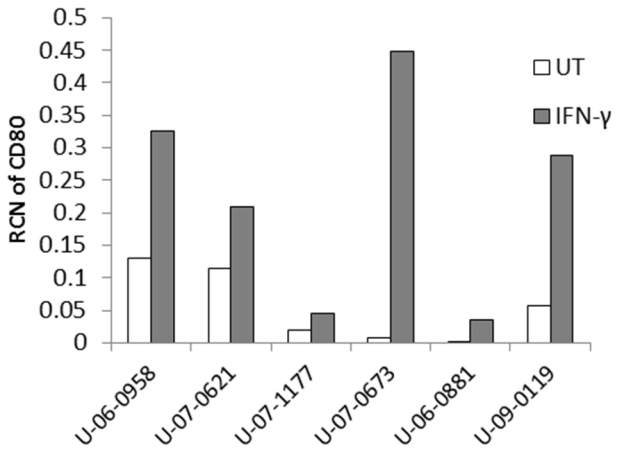
Daratumumab is a first-in-class anti-CD38 monoclonal antibody approved for treatment of refractory multiple myeloma; encouraging responses with an acceptable safety profile were seen in heavily pre-treated patients[12,13]. Daratumumab has been shown to also have immunomodulatory effects on T cell subsets; increased T cell numbers ($CD8^+$ cells) in both peripheral blood and bone marrow were observed following Daratumumab treatment. Responders had higher numbers of CD8+ t cells than non-responders, which was most pronounced after Cycle 3. A highly immunosuppressive subset of T-regs expressing CD38 decreased significantly following Daratumumab treatment[14].

In addition to the T cell effects, we have discovered that CD38 antibody-binding to AML cells can encourage cell-to-cell killing or fratricide. This is consistent with the fact that AML cells (both primary and cell lines) express Fc gamma Receptors much like fully differentiated monocytes and macrophages, and are capable of antibody-mediated destruction of target cells albeit at a lower efficiency[15]. Below, we provide data attesting this hypothesis.

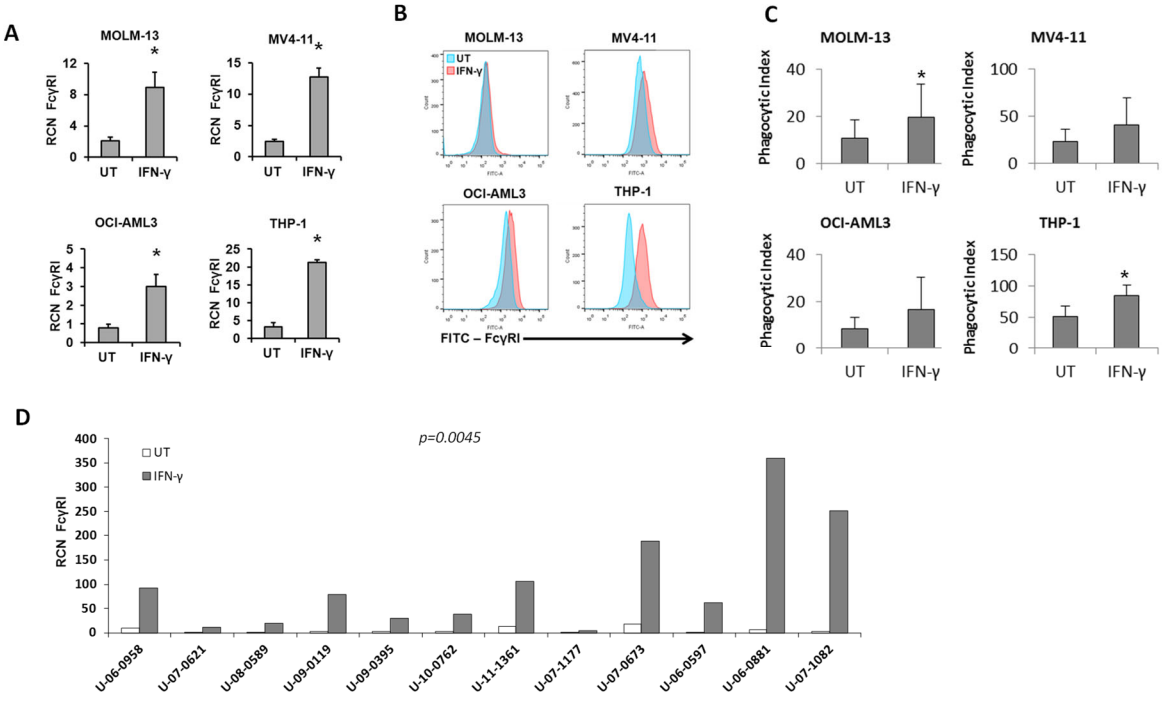
**Methods**: Primary patient samples were obtained from apheresis when patients presented with high white blood cell counts and required leukapheresis. AML cell lines MOLM-13, THP-1, OCI-AML3 and MV4-11 were also used. Commercial anti-CD38 antibodies were used for these experiments.

Results:

***I.*** ***IFN-γ promotes an activated M1 phenotype in AML cells***. Myeloid cells within the context of tumors commonly display M2-like characteristics, which serves to promote tumor growth and survival. Here, we tested whether treatment with IFN-γ could skew AML cells toward an M1 phenotype. We treated the AML cell lines MOLM-13, MV4-11, OCI-AML3 and THP-1 overnight with or without IFN-γ and measured expression of the M1 markers CD80 and CD86. Results showed that overnight treatment with IFN-γ significantly increased the expression in all 4 cell lines of both CD80 and CD86 (data not shown). We also verified increased surface expression of CD86 via flow cytometry (data not shown). Next, we treated samples from AML patients overnight with versus without IFN-γ and measured the expression of these markers. Results showed that transcripts for both CD80 (Figure 1) and CD86 (data not shown) were significantly increased.

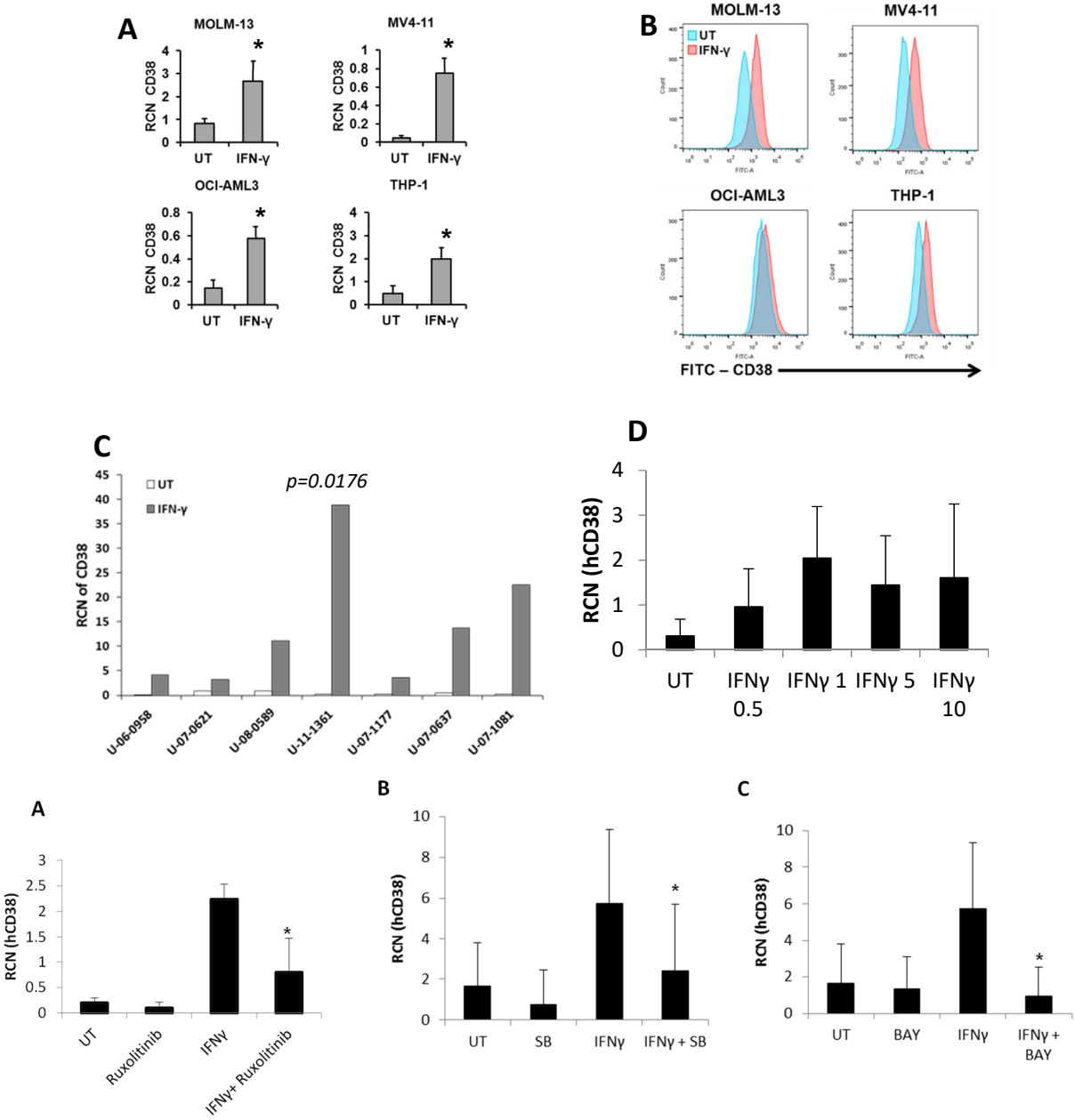


***II.*** ***IFN-γ increases FcγRI expression and phagocytic ability in AML cells***. It has previously been shown that IFN-γ could increase the expression of FcγR1 in AML cells which led to the investigation of IFN-γ treatment combined with drug-conjugated anti-FcγRI antibody as a potential therapy for AML. Here, we explored the possibility that IFN-γ treatment would not only increase FcγRI but would also enhance the phagocytic ability of these AML cells, as FcγRI is a major effector of phagocytosis in myeloid cells. For this, we first treated the AML cell lines MOLM-13, MV4-11, OCI-AML3 and THP-1 overnight with or without IFN-γ and measured FcγRI expression by qPCR and flow cytometry. Results showed that, as expected, IFN-γ significantly increased both the transcript (Figure 2A) and surface expression (Figure 2B) of FcγRI. Next, we treated the cell lines overnight as above, and then subjected them to a phagocytosis assay using antibody-opsonized sheep red blood cells as targets. As shown in Figure 2C, IFN-γ treatment significantly enhanced the phagocytic ability of MOLM-13 and THP-1, with MV4-11 and OCI-AML3 showing a trend toward enhancement. We then tested the effects of IFN-γ on patient samples and found that it significantly increased FcγRI expression (Figure 2D). These results indicate that IFN-γ can enhance not only the expression, but also the function, of FcγR in AML cells.




***III.*** ***IFN-γ increases CD38 expression in AML cells.*** Internalization of therapeutic antibodies by the tumor cells is beneficial within the context of antibody-drug conjugates, but such internalization also reduces the ability of immune effector cells to bind and destroy the targets. CD38 is currently being investigated as an antigen that shows less internalization than CD33, thereby potentially serving as a superior target for effector cell-mediated ADCC. Hence, we measured the expression of CD38 on these cells. To do this we treated the AML cell lines MOLM-13, MV4-11, OCI-AML3 and THP-1 overnight with or without IFN-γ and then measured levels of CD38. Results showed that IFN-γ treatment led to a significant increase in CD38 in all cell lines tested, as measured by qPCR (Figure 3A) and by flow cytometry (Figure 3B). We next tested AML patient samples in similar fashion and found that IFN-γ significantly increased CD38 expression in these cells as well (Figure 3C). Hence,

not only does IFN-γ promote FcγR expression and function in AML cells, it also increases the expression of a candidate antigen target for antibody therapy. Next, to test which concentration of IFN-γ was required for this up-regulation of CD38, we treated AML patient apheresis samples overnight with 0-10 ng/ml IFN-γ and measured CD38 via qPCR. Results showed that as little as 0.5 ng/ml was sufficient to elicit a significant increase in CD38.



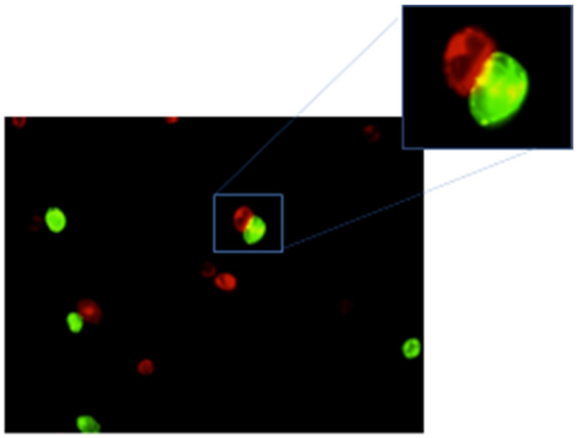

***IV.*** ***<u>IFN-γ-mediated CD38 up-regulation requires activation of Jak/Stat, p38 and NF-κB.</u>*** In order to determine which downstream signaling pathways were required for the up-regulation of CD38 seen

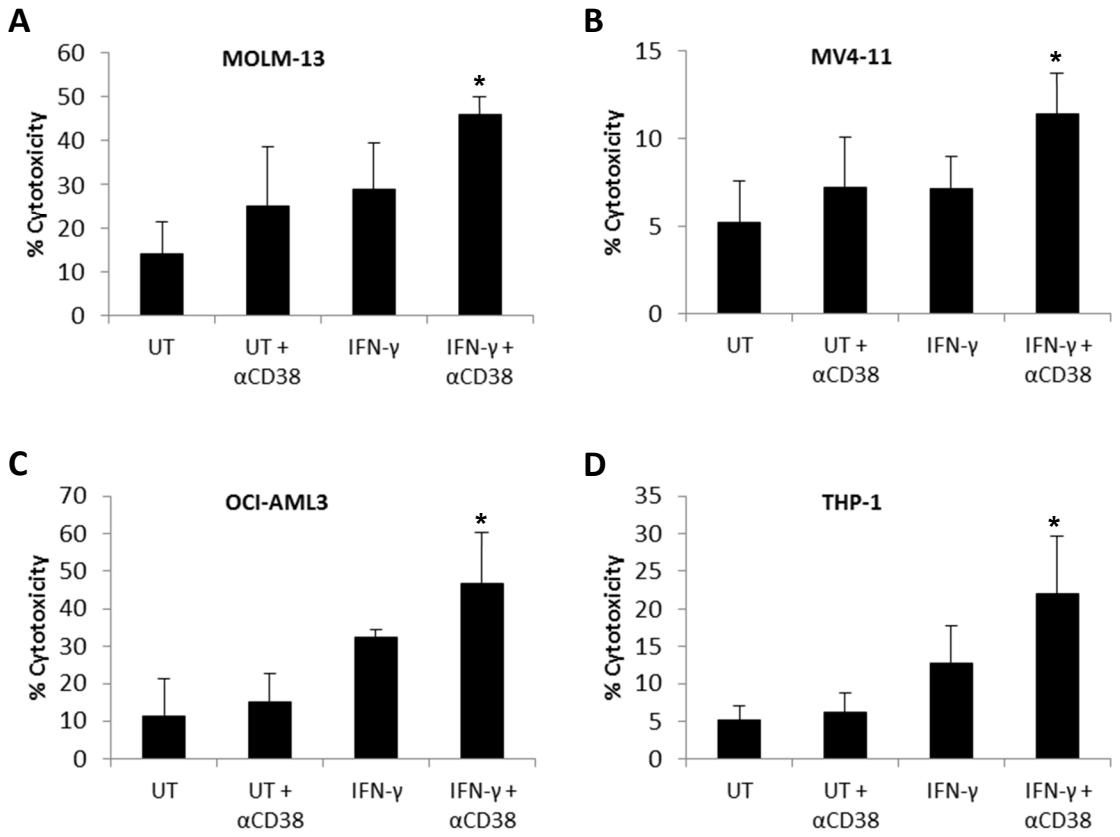
with IFN-γ treatment, we pre-treated AML patient apheresis samples with inhibitors for Erk, PI3K, p38 MAPK, Jak/STAT and NF-κB. Results showed that IFN-γ-mediated up-regulation of CD38 was significantly stunted in cells treated with inhibitors for Jak/Stat, p38 and NF-κB (Figures 4A, B and C, respectively), but not with inhibitors of the PI3K and Erk pathways.

***V.*** ***IFN-γ enhances antibody-mediated fratricide in AML cells***. Results have shown that IFN-γ of AML cells could promote their shift toward an M1 phenotype, could enhance the expression and function of FcγR, and could also increase the expression of an antigen target for antibody therapy. This led us to test whether IFN-γ treatment could promote an antibody-mediated killing of AML cells by one another, a phenomenon termed fratricide. To test this we first examined whether IFN-γ-treated and antibody-opsonized THP-1 cells could form conjugates between one another. For this THP-1 cells were primed overnight with 10 ng/ml IFN-γ. Cells were then labeled with either PKH-67 (green) or Claret (red) dye (Sigma Aldrich). The green-labeled cells were then incubated on ice for 60 minutes with 10 μg/ml anti-CD38, washed and mixed at a 1:1 ratio (red: green). Following 3 hour incubation at 37 °C, cells were washed, fixed in 4% paraformaldehyde and analyzed by fluorescence microscopy using a red/green dual-filter objective (Figure 5A). The number of antibody-dependent conjugates (Green-Red and Green-Green) and non-specific conjugates (red-red) was scored in a blinded fashion (Figure 5B). The results demonstrate that indeed THP-1 cells attach to one another in an antibody-dependent manner.

***VI.*** ***CD38 antibody-opsonized cells engage in fratricide.***

We treated the AML cell lines MOLM-13, MV4-11, OCI-AML3 and THP-1 overnight with or without IFN-γ, then incubated them for an additional 18 hours with anti-CD38 antibody and measured cell death via LDH assays. As shown in Figures 6A-D, IFN-γ significantly enhanced the antibody-mediated killing within each respective AML cell line. To test whether this was due to a toxic effect of anti-CD38, we incubated the AML cell lines on immobilized anti-CD38 for the same length of time and found that LDH release was not affected (data not shown). This suggests that the anti-CD38 antibody led to cell-against-cell killing, which was triggered and enhanced by IFN-γ pre-treatment.






## 4.4 RATIONALE FOR PROPOSED STUDY

CD38 expression has been demonstrated on a small subset of leukemic stem cells which are thought to be the reservoir for leukemic relapse. Daratumumab is an FDA approved antibody targeting CD38 in multiple myeloma. AML is not an indication approved by the FDA for Daratumumab. Apart from CD38 targeting, Daratumumab also has immunomodulatory effects increasing the recruitment of T cells into the marrow[16]. Preclinical studies from OSU have shown the efficacy of Daratumumab in AML when used in combination with IFN-gamma which has resulted in upregulation of CD38. IFN-γ promotes graft-versus-leukemia effects without directly interacting with leukemia cells in mice after allogeneic hematopoietic cell transplantation[17,18]. IFN-gamma levels are elevated in post-transplant patients post-conditioning, infections, GVHD, and during hematopoietic regeneration.

Donor lymphocyte infusion is associated with a 15-30% chance of inducing remission but can be associated with GVHD. CD38 has also been shown to be an early biomarker for development of GVHD.

We hypothesize that **(i) IFN-gamma levels will be higher in post-transplant patients than healthy donors and (ii) combination of Daratumumab and endogenous IFN-gamma will mediate antileukemic efficacy post-transplant (iii) the combination of Daratumumab and donor lymphocytes will provide potent effectors (T cells and NK cells), recruit effectors to marrow and mediate graft-versus-leukemia effect.**

# 5 STUDY OBJECTIVES

## 5.1 PRIMARY OBJECTIVE

**Primary Objective for Phase I study:**

To determine the maximum tolerated dose (MTD) of Daratumumab and escalating doses of donor lymphocyte infusions (DLI) in post-HCT patients with relapsed AML and MDS transformed to AML.

**Primary Objective for Phase II study:**

To evaluate overall response rate to Daratumumab and DLI by week 8 in patients with post-HCT relapsed AML and MDS

## 5.2 SECONDARY OBJECTIVES

1. To assess overall response rates in MRD positive patients and in patients with overt morphological relapse
2. To assess MRD conversion rates from MRD positive to MRD negative.
3. To determine the post-relapse 6-month OS rates of patients with relapsed AML and MDS following Allo-HSCT who are treated with Daratumumab
4. To determine the rates of GVHD (both grades II-IV and III-IV) and autoimmune side effects of Daratumumab within 3 months of completion of study
5. To determine the post-relapse 6-month PFS rates of patients with relapsed AML and MDS following Allo-HSCT who are treated with Daratumumab

## 5.3 EXPLORATORY OBJECTIVES

1. To compare CD38 expression levels in myeloid blasts and IFN-γ levels in plasma, by flow cytometry and PCR, at the time of relapse before starting Daratumumab and at progression or relapse after Daratumumab To compare peripheral blood T cell number and subsets (CD3, CD4, CD8, CD38 expression on T-regs, CD4 and CD8), T regs, B-regulatory cells, NK cell numbers and bone marrow T cell subsets, by flow cytometry, at the time of relapse before starting Daratumumab, at the time of partial/complete response to Daratumumab, and at the time of progression or relapse after Daratumumab
2. To evaluate whether Daratumumab has (i) Direct anti-leukemia effects by measuring the expression of the M1 markers CD80 and CD86 by flow cytometry and PCR (ii) Antibody-dependent cellular cytotoxicity (ADCC) and Antibody-dependent cellular phagocytosis (ADCP) by using chromium based ADCC assays, and a phagocytosis assay using antibody-opsonized sheep red blood cells as targets and (iii) Immune modulation of autologous immune system (NK cells, T cells, T-regs, B-regs, and MDSCS) in AML
3. To evaluate the effect of Daratumumab on exosome content and clearance along with other soluble factors in AML
4. To evaluate serum IFN levels pre- Daratumumab, during and post-Daratumumab
5. To evaluate whether fratricide occurs in patients treated with Daratumumab

# 6 STUDY ENPOINTS

## 6.1 PRIMARY ENDPOINT

**Phase I study:** Safety and feasibility of combination of Daratumumab and donor lymphocyte infusion.

**Phase II study:** Overall response rate to Daratumumab and DLI in patients with post-HCT relapsed AML and MDS

## 6.2 SECONDARY ENDPOINTS FOR PHASE II

ORR in MRD positive patients and in patients with overt morphological relapse

MRD conversion rates

- 6 month post-relapse progression-free survival
- 6 month post-relapse overall survival
- 3 month GVHD rate

## 6.3 EXPLORATORY ENPOINTS FOR PHASE I AND II

Samples will be retained and/or stored for potential future use in the OSU – Leukemia Tissue Bank for up to 10 years after completion of study. Samples will be coded to protect subject identify and only the PI (Dr. Vasu) will have access to the samples. All correlative studies will be conducted only at Ohio State University.

**Bone marrow:**

1. Expression of CD38 on bone marrow: CD38 expression and other phenotypic markers on bone marrow is checked prior to transplant. Most patients are in remission prior to transplant. Patients who were initially treated at OSU will have banked leukemia samples at the time of diagnosis. Expression of CD38 on samples at diagnosis and prior to transplant will be evaluated by flow cytometry.
2. Expression of CD38 in lymphocytes in bone marrow: Percentage of lymphocytes in bone marrow pre- and post-treatment with Daratumumab will be studied. In addition to percentage, expression of CD38 on lymphocytes will be evaluated by flow cytometry.
3. Phenotypic studies to evaluate T cell exhaustion/function will be performed on bone marrow samples pre-and post-treatment with Daratumumab at the specified time points
4. Phenotypic studies to evaluate activation status of NK-cells will be performed on bone marrow samples pre-and post-treatment with Daratumumab
5. T-cell, NK cell, B-cell, and MDSC infiltration in bone marrow will be evaluated on bone marrow samples pre-and post-treatment with Daratumumab
6. Exosomes from bone marrow will be examined at these serial times for both number and also content (protein, mRNA, and mIRs)
7. Serial assessment of microenvironment with stromal cell cultures.
8. Three tubes from bone marrow will be collected at each time point.

**Peripheral blood:**

1. Chimerism analysis: Using single-nucleotide polymorphisms, relative contributions from donor vs. recipient in sorted $CD3^+$ and $CD33^+$ cells will be measured and expressed as a percentage.
2. Immune reconstitution: Dr. Gerard Lozanski has developed a panel called the Immunome to study reconstitution of T cells, NK cells and B cells post-transplant. Specific information regarding stages of activation of T cells is also available from this panel.
3. Immune response post Daratumumab: The Immunome panel will be performed at the following time points: Day 90, 180 and 365 (+/- 7days).

4. Phenotypic studies to evaluate T-cell exhaustion will be performed on bone marrow samples pre- and post-treatment with Daratumumab
5. Phenotypic studies to evaluate activation status of NK-cells will be performed on bone marrow samples pre-and post-treatment with Daratumumab
6. Measurements of cytokines including but not limited to IFN- γ will be measured at relapse, pre and post Daratumumab treatment.
7. Exosomes from bone marrow will be examined at these serial times for both number and also content (protein, mRNA, and mIRs).
8. CD38, CD55, and CD59 expression in circulating blood cells will be evaluated
9. Three tubes of blood will be collected at each time point for correlative studies.

# 7 STUDY DESIGN

## 7.1 OVERVIEW OF STUDY DESIGN

This is a phase I/II study that evaluates combination of Daratumumab and escalating doses of donor lymphocyte infusions. Donor lymphocyte infusions will be given within 72 hrs. of daratumumab dose. The following dose levels are used.

1. Phase I study with the following dose levels for related sibling donors:
    a. Dose level 1: Dara 16mg/kg
    b. Dose level 2: Dara 16mg/kg + DLI (1 infusion at any time between weeks 3-5) : 1x10e6 CD3/kg
    c. Dose level 3: Dara 16mg/kg + DLI (1 infusion at any time between weeks 3-5): 1x10e7 CD3/kg
2. Phase I study with the following dose levels for unrelated donors:
    c. Dose level 1: Dara 16mg/kg
    d. Dose level 2: Dara 16mg/kg + DLI (1 infusion at any time between weeks 3-5): 1x10e5 CD3/kg
    e. Dose level 3: Dara 16mg/kg + DLI (1 infusion at any time between weeks 3-5): 1x10e6 CD3/kg
3. Phase I study with the following dose levels for haploidentical donors:
    f. Dose level 1: Dara 16mg/kg
    g. Dose level 2: Dara 16mg/kg + DLI (1 infusion at any time between weeks 3-5): 1x10e4 CD3/kg
    h. Dose level 3: Dara 16mg/kg + DLI (1 infusion at any time between weeks 3-5): 1x10e5 CD3/kg

Patients with MRD will not be enrolled until the DLT period for dose level 1 has been completed and it has been determined that the treatment schedule is safe. Patients must be positive for MRD disease as

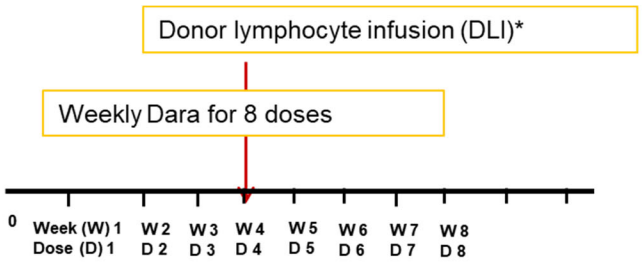
determined by the combined analyses of flow cytometry, genomic sequencing and cytogenetics. Patients who do not demonstrate evidence of MRD in all three methods will not be eligible for the trial.

Bone marrow biopsies are done at the completion of 8 weeks. The maximal tolerated dose of DLI is chosen for expansion to the phase II portion of the study.

If patients are found to be in CR at the end of 8 weeks and treating physician concludes that patient continues to benefit from treatment, patients may proceed to Daratumumab maintenance with a schedule of 16mg/kg every 2 weeks for 16 weeks (8 doses) and then monthly for 6 months .

For patients with rapidly progressive disease despite 4 doses of Daratumumab, they will come off trial.

The dose level that is deemed safe will be chosen for the phase II portion of the study.




| Dose level | Sibling donor | Unrelated donor | Haploidentical donor |
|---|---|---|---|
| Dose level 1 | Dara 16mg/kg | Dara 16mg/kg | Dara 16mg/kg |
| Dose level 2 | Dara 16mg/kg + DLI at weeks 3-5: 1x10e6 CD3/kg | Dara 16mg/kg + DLI at weeks 3-5: 1x10e5 CD3/kg | Dara 16mg/kg + DLI at weeks 3-5: 1x10e4 CD3/kg |
| Dose level 3 | Dara 16mg/kg + DLI at weeks 3-5: 1x10e7 CD3/kg | Dara 16mg/kg + DLI at weeks 3-5: 1x10e6 CD3/kg | Dara 16mg/kg + DLI at weeks 3-5: 1x10e5 CD3/kg |

## 7.2 NUMBER OF PATIENTS

For phase I, we expect to enroll a minimum of 3 and a maximum of 18 patients for the related donor portion and 3-18 patients for the unrelated donor cohort. Accounting for 10% unevaluable for DLT, we expect 4-20 patients for each cohort in summary we expect 8-40 patients for phase I portion of the study. Enrollment can occur in parallel for both related and unrelated donor arms of the study. For Phase II, we will expect to enroll 25 patients.

## 7.3 DURATION OF STUDY

For phase I related donor arm, we expect the study duration between 10 months to 3.5 years including DLT observation period, while for the unrelated donor arm, it will take about 8 months to 2.5 years. For phase II, the study duration will be around 2 years including following up period.

# 8 STUDY POPULATION

## 8.1 INCLUSION CRITERIA

1. Age ≥ 18 years
2. AML or MDS relapse following Allo-HSCT (Morphological relapse, or MRD positive by flow cytometry, cytogenetics, and molecular mutations)
3. Patients who received a 10/10 HLA-matched allogeneic HCT either from sibling donors or unrelated donors or at least a 5/10 haploidentical transplant for Dose level 2 and 3
4. Patients with R/R AML must not be candidates for available therapies known to be effective for treatment of their AML.
5. For patients in Dose level 1 (Daratumumab only), relapsed refractory AML patients who have previously not received an allogeneic HCT are eligible.
6. Engraftment must have occurred as defined by platelet (PLT) count > 20,000/μL and ANC ≥ 0.5
7. ECOG performance status < 3
8. Creatinine clearance > 40 ml/min (Calculated or measured)
9. Aspartate aminotransferase (AST) < 3 x upper limit of normal (ULN), alanine aminotransferase (ALT) < 3 x ULN, and total bilirubin < 1.5 x ULN
10. Off calcineurin inhibitors for at least 2 weeks
11. Prednisone dose ≤ 20 mg/day.
12. Patients with proliferative disease can be cytoreduced with cytotoxic chemotherapy at investigator's discretion, but there should be at least a 14 day window between start of cytoreductive therapy and start of Daratumumab
13. Blast count < 20 K/day (hydrea use is allowed)
14. Patient willing to agree to study-related research marrows
15. Female patients of childbearing potential who are sexually active must be willing to use an effective barrier method of birth control to avoid pregnancy during the study and for a minimum of 3 months after stopping study treatment
16. Male patients with partners of childbearing potential who are sexually active must be willing to use an effective barrier method of birth control to avoid pregnancy during the study and for a minimum of 3 months after stopping study treatment

## 8.2 EXCLUSION CRITERIA

1. No demonstrable evidence of donor chimerism (< 55 donor CD3 or CD33 chimerism)
2. Patients with a molecular mutation without chromosomal abnormalities or declining chimerisms (MRD status must be verified by surface marker and mutational analyses)
3. Active graft-versus-host disease (GVHD) grades I-IV; prior acute GVHD could have occurred but resolved at time of initiation of Daratumumab
4. Extensive chronic GVHD requiring ongoing immunosuppression with calcineurin inhibitors or more than 20 mg of prednisone
5. Patients with FLT3+ AML or blast crisis CML who have not yet received post-transplant TKI therapy

6. Active CNS or testicular disease
7. Subject is:

7.2 seropositive for human immunodeficiency virus (HIV)

7.3 seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

8. seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
9. Patients must not have chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) < 50% of predicted normal. FEV1 is required for patients suspected of having chronic obstructive pulmonary disease and are not eligible if FEV1 is < 50% of predicted normal.
10. Patients must not have moderate or severe persistent asthma within the past 2 years and must not have currently uncontrolled asthma of any classification.
11. Active autoimmune disease prior to transplant
12. Female patients of childbearing potential who are sexually active and unwilling to use an effective barrier method of birth control to avoid pregnancy during the study and for a minimum of 3 months after study treatment.
13. Male patients with partners of childbearing potential who are sexually active and unwilling to use an effective barrier method of birth control to avoid pregnancy during the study and for a minimum of 3 months after study treatment
14. Concurrent use of any other investigational drugs

# 9 DARATUMUMAB ADMINISTRATION

Daratumumab will be dosed at 16mg/kg following guidelines provided in package insert. For management of infusion-related toxicities, see 9.2.

## 9.1 RECOMMENDED CONCOMITANT MEDICATIONS

### 9.1.1 Pre-infusion Medication

Administer pre-infusion medications to reduce the risk of infusion reactions to all patients 1-3 hours prior to every infusion of Daratumumab per OSU guidelines

### 9.1.2 Post-infusion Medication

Administer post-infusion medication to reduce the risk of delayed infusion reactions to all patients as follows according to OSU guidelines.

In addition, for any patients with a history of chronic obstructive pulmonary disease, consider prescribing post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids. Following the first four infusions, if the patient experiences no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

## 9.2 DARATUMUMAB INFUSION RELATED REACTIONS

For infusion reactions of any grade/severity, immediately interrupt the DARATUMUMAB infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of DARATUMUMAB as outlined below.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour.
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as clinically appropriate. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARATUMUMAB upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life threatening): Permanently discontinue Daratumumab treatment.

## 9.3 DONOR LYMPHOCYTE INFUSION

Donor lymphocytes are typically infused as outpatient according to institutional guidelines. To allow for scheduling ease, DLI will be infused within 72 hrs. after the daratumumab dose, anytime between week 3-4. .

## 9.4 CRITERIA TO BE MET BEFORE EACH DOSE OF DARATUMUMAB

Patients need to be evaluated with documentation of the following before starting each dose of Daratumumab:

1. Patient is hemodynamically stable without concern for active infection
2. No evidence of active GVHD
3. Prednisone dose is ≤ 20mg/day.

## 9.5 POST-TRANSPLANT STANDARD OF CARE CONCOMITANT MEDS

Patients are recommended to be on ursodiol (Actigall) for liver protection. Patients will also be on antifungal prophylaxis (posaconazole is preferred), antiviral prophylaxis (acyclovir or valacyclovir) and anti-PCP prophylaxis (dapsone, Bactrim).

## 9.6 DEFINITIONS OF DOSE LIMITING TOXICITY

Dose limiting toxicity would be development of Grade 3-4 GVHD. GVHD will be graded according to the Glucksberg criteria.

Dose-limiting toxicity is defined as:

- Grade 3-4 Acute GVHD
- Any Grade 3-4 non-hematologic toxicity related to Daratumumab
- Hematologic toxicity: grade 4 toxicity not related to the underlying disease and not responding to growth factor or transfusion within 7 days

Grade 3 or higher non-neurologic immune-related adverse events (e.g. diarrhea, pruritus, rash) that respond to corticosteroids and improve to grade 1 or less within 4 weeks will NOT count as DLTs. Optional biopsy of affected organs will be encouraged to help determine whether the immune-related condition is due to GVHD. Once a patient develops Grade 3-4 GVHD, further enrollment will be on hold until safety and monitoring committee assesses toxicity.

For patients developing Grade 2 GVHD, further doses of Daratumumab will be held until GVHD is controlled. Patients have to meet above-listed criteria before they can resume Daratumumab.

In the phase II expansion part of the study, if >2 patients develop ≥ Grade 3 GVHD, we will stop enrollment and reassess safety.

# 10 MANAGEMENT OF CLINICAL EVENTS

## 10.1 CYTOPENIAS

Bone marrow biopsies will be done at time of consent, prior to DLI and at week 8. Additional Bone marrow biopsies can be done at any time at discretion of treating physician. If bone marrow shows persistent disease, cytopenias would be attributed to persistent leukemia.

Transfusions will follow institutional guidelines which typically are to keep Hgb> 7gm/dL and platelet (PLT) count more than 10K/µl.

## 10.2 GRAFT VERSUS HOST DISEASE

Patients will be assessed for GVHD at every visit, for new diagnosis of suspected GVHD, biopsy will be done whenever feasible. Management of GVHD will follow guidelines listed in the Programmatic approach to management of GVHD followed at the James.

## 10.3 OTHER CLINICAL EVENTS

For any grade 3-4 non-hematologic event observed, treating physician will determine relatedness as follows:

- ☐ Related to leukemia
  - ☐ Definitely
  - ☐ Probably
  - ☐ Possibly
  - ☐ Unlikely
  - ☐ Unrelated
- ☐ Related to transplant
  - ☐ Definitely
  - ☐ Probably
  - ☐ Possibly

- ☐ Unlikely
- ☐ Unrelated

☐ Related to Daratumumab – if Yes, fill one of the boxes below

- ☐ Definitely
- ☐ Probably
- ☐ Possibly
- ☐ Unlikely
- ☐ Unrelated

☐ Related to DLI

- ☐ Definitely
- ☐ Probably
- ☐ Possibly
- ☐ Unlikely
- ☐ Unrelated

Is event expected - Yes or No

# 11 DESCRIPTION OF INVESTIGATIONAL AGENT

## 11.1 STORAGE, HANDLING AND ACCOUNTABILITY

Daratumumab is a colorless to pale yellow, preservative-free solution for intravenous infusion supplied as:
NDC 57894-502-05 contains one 100 mg/5 mL single-dose vial
NDC 57894-502-20 contains one 400 mg/20 mL single-dose vial

**Storage and Stability**
Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze or shake. Protect from light. This product contains no preservative.

## 11.2 SAFTEY INFORMATION FOR DARATUMUMAB

Daratumumab is a CD38-directed cytolytic antibody that is FDA approved for multiple myeloma. Safety information was obtained from the package insert (https://www.darzalexhcp.com/shared/product/darzalex/darzalex-prescribing-information.pdf and shown below:

1. Infusion reactions: Interrupt Daratumumab infusion for infusion reactions of any severity. Permanently discontinue the infusion in case of life-threatening infusion reactions.

2. Interference with cross-matching and red blood cell antibody screening: Type and screen patients prior to starting treatment. Inform blood banks that a patient has received Daratumumab

3. Neutropenia: Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Dose delay may be required to allow recovery of neutrophils.

4. Thrombocytopenia: Monitor complete blood cell counts periodically during treatment. Dose delay may be required to allow recovery of platelets.

The most frequently reported adverse reactions (incidence ≥20%) in clinical trials were: infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, muscle spasms, back pain, pyrexia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy and upper respiratory tract infection

Patients with AML or MDS transformed to AML have pre-existing thrombocytopenia and neutropenia; abnormalities in blood counts will be attributed to underlying disease.

The effects of Daratumumab on the developing fetus/embryo is not known. Patients will be counselled to use effective contraception methods after transplant and specifically during the time period of study participation and study follow-up.

# 12 STUDY CONDUCT

## 12.1 STUDY PROCEDURES

### 12.1.1 PHYSICAL EXAMINATION

A focused physical exam pertaining to vitals and assessment for GVHD will be performed at time of enrollment and prior to each dose of Daratumumab.

### 12.1.2 LABORATORY EVALUATION

At screening:

1. CBC, CMP, LDH, Type and cross with DAT, pregnancy test( if applicable)

2. CD3, CD33 peripheral blood chimerisms

Prior to Each dose of Daratumumab:

1. CBC, CMP

End-of-study visit

1. CD3 CD33 peripheral blood chimerisms

Long-term follow-up to 6 months will occur – at month 3 and at month 6. These visits will be done when patient is evaluated by their treating physician.

12.1.3 STUDY RELATED PROCEDURES AND STUDY CALENDAR

| | Screening[a] | Pre-1st Dose Daratumumab | Post-1st Dose Daratumumab | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Long Term Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 3 or 4 | Day 8 | Day 15 | Day 22 | Day 29 | Day 36 | Day 43 | Day 50 | Day 57-71 |
| Informed Consent | X | | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Physical Exam & Vital Signs | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy Test (if applicable) | X | | | | | | | | | | |
| Medication Record | X | | X | X | X | X | X | X | X | X | X |
| Performance Status | X | | X | X | X | X | X | X | X | X | X |
| Blood Draw (Complete Blood Count) | X | X | X | X | X | X | X | X | X | X | X |
| Blood Draw (Complete Metabolic Panel) | X | | X | X | X | X | X | X | X | X | X |
| GVHD Assessment | X | X | X | X | X | X | X | X | X | X | X |
| Donor Lymphocyte Infusion (DLI) | | | | | | X | | | | | |
| Adverse Event Monitoring | X | X | X | X | X | X | X | X | X | X | X |
| Bone Marrow Biopsy | X | | | | | (Pre-DLI) X | | | | | X |
| Research Bone Marrow samples (3 green tops of 6 ml each) | X | | | | | X | | | | | X |
| Research blood samples (2 green tops(6 ml each) and one red top (6 ml)) | X | X | X | x | X | X | x | X | X | x | |

[a] Screening window is 28 days.

The bone marrow biopsy at week 4 can be done at week 3, but it has to be done before the DLI. So, if the DLI can be arranged at week 4, then the marrow will be done week 3. For patients deemed eligible to receive maintenance therapy, the following procedures will be performed. Daratumumab will be administered if PLT count is > 100K and ANC> 500.

| | **Start of Daratumumab Maintenance [a]** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week [b] | Week 9 | Week 11 | Week 13 | Week 15 | Week 17 | Week 19 | Week 21 | Week 23 | Week 25 | Week 29 | Week 33 | Week 37 | Week 41 | Week 45 |
| CBC | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Vital signs | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| GVHD assessment | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Performance status | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Adverse event monitoring | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

a) Daratumumab maintenance, a schedule of 16mg/kg every 2 weeks for 16 (8 doses) weeks and then monthly for 6 months will be given.
b) Daratumumab can be given +/- 3 days but there has to be a week interval between doses.
marrow during Daratumumab maintenance is at the discretion of the physician and will be considered standard of care.

## TIME AND EVENTS SCHEDULE OVERVIEW

| | **Screening Phase** | **Treatment Phase** | | **Follow-up Phase** | | **Notes** |
|---|---|---|---|---|---|---|
| | Within 28 days of daratumumab | Day 1 of each cycle (28-day cycles) | EOT within 30 days of last dose | Prior to PD | After PD (every 6 months) | |
| **Laboratory Assessments** | | | | | | |
| Hepatitis B (HBV) serology | X | | | | | Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc).<br><br>Refer to Section 12.1.3 |
| HBV DNA testing | X | Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment | | | | For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally.<br><br>Refer to Section 12.1.3. |

## Concomitant therapy

### Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

## STUDY EVALUATIONS

### HBV Serology

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment v.3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

### HBV DNA Tests:

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Table 12.1.3). Where required by local law, the results of HBV testing may be reported to the local health authorities.

## 12.2 DISEASE ASSESSMENT TIMELINES

Disease assessment will be performed at the following time points:

Screening for trial

Bone marrow biopsy pre-DLI

End of study bone marrow biopsy

In addition, bone marrow biopsies can be performed at the discretion of the primary physician.

## 12.3 COMPLETION OF TREATMENT

Treatment with study drug may be discontinued for any of the following reasons:

Adverse event.

Protocol violation.

Unsatisfactory therapeutic response.

Study terminated by sponsor.

Withdrawal by subject.

Lost to follow-up.

Other

## 12.4 COMPLETION OF STUDY

Patients will be considered to have completed the study

1. If they withdrew from the study
2. Come off study due to progressive disease

3.Complete the 6 month follow up period after completion of treatment

## 12.5 POST-TREATMENT FOLLOW-UP ASSESSMENTS

Patients who remain in remission will be followed for development of acute and chronic GVHD and safety during clinic visits for at least 12 months after study treatment or until the patient's death or withdrawal of consent or termination of the study by the sponsor.

All patients will be followed for OS until death, withdrawal of consent, termination of study by the sponsor, or for a maximum of 1 year after until the last patient is enrolled in the study. Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (e.g., social security indexes).

## 12.6 EXPECTED TIMELINES FOR RECRUITMENT, DATA REPORTING

First patient enrollment: February 2019?

# 13 ADVERSE EVENT MONITORING AND REPORTING

Adverse events of special interest are events that the COMPANY is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- HBV Reactivation
- Other malignancies

Any Adverse Event of Special Interest that is to be reported to the COMPANY should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of knowledge of the event**.

## 13.1 Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a J&J medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected J&J medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- J&J protocol ID

## 13.2 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., auto injector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

## 13.3 Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

**NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.**

13.3.1 Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

13.3.2 Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

**1. Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

For DARZALEX™ (daratumumab),the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

**2. Special Reporting Situations**

Safety events of interest for a J&J medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product
- Inadvertent or accidental exposure to a J&J medicinal product
- Medication error (includes potential, intercepted or actual) involving a J&J product (with or without patient exposure to the J&J Product(s) Under Study, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a J&J medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a J&J medicinal product

These safety events may not meet the definition of an adverse event; however, from a COMPANY perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of becoming aware of the event.**

## 13.4 PREGNANCY

All initial reports of pregnancy must be reported to COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the J&J medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a J&J medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

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

## 13.5 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The Ohio State University and PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at COMPANY's request.

## 13.6 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for J&J medicinal products to the COMPANY

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a J&J medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a J&J medicinal product.

All (serious and non-serious) adverse events reported for a J&J medicinal product should be followed-up in accordance with clinical practice.

### 13.6.1 SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The Ohio State University and the PRINCIPAL INVESTIGATOR will transmit all SAEs and special situations following exposure to a J&J product under study in a form provided by the COMPANY in accordance with Section 10, Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, to COMPANY using COMPANY's Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

- The Ohio State University and/or PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

  Copies of any and all relevant extraordinary (not including routine initial or follow-up ICSR submission) correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the J&J Product under study, are to be provided COMPANY using a transmission method in Section 8within **24 hours of such report or correspondence being sent to applicable health authorities.**

13.6.2 Non-Serious AEs
All non-serious adverse events should be reported to COMPANY according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

13.6.3 PQC Reporting
A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and COMPNAY, and are mandated by regulatory agencies worldwide. COMPANY has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a J&J medicinal product under study must be reported to COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The COMPANY contact will provide additional information/form to be completed.

If the defect for a J&J medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

**3. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-J&J Medicinal Products**

For SAEs, special reporting situations and PQCs following exposure to a non-J&J medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

**4. Transmission Methods**

The following methods are acceptable for transmission of safety information to the COMPANY:

- Electronically via J&J SECURE Email service (preferred) , to **IIS-BIO-VIRO-GCO@its.jnj.com**
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report, to **1-866-451-0371**
- Telephone (if fax is non-functional)

Every adverse event will follow the same reporting Guidelines: For any grade 3-4 non-hematologic event observed, treating physician will determine relatedness as follows:

☐ Related to leukemia

- ☐ Definitely
- ☐ Probably
- ☐ Possibly
- ☐ Unlikely
- ☐ Unrelated

☐ Related to transplant

- ☐ Definitely
- ☐ Probably
- ☐ Possibly
- ☐ Unlikely
- ☐ Unrelated

☐ Related to Daratumumab – if Yes, fill one of the boxes below

- ☐ Definitely
- ☐ Probably
- ☐ Possibly
- ☐ Unlikely
- ☐ Unrelated

☐ Related to DLI

- ☐ Definitely
- ☐ Probably

- ☐ Possibly
- ☐ Unlikely
- ☐ Unrelated

Is event expected - Yes or No

# 14 STUDY-SPECIFIC COMMITTEES

## 14.1 DOSE ESCALATION AND ADVERSE EVENT MONITORING CALLS

Once a patient is enrolled, safety and monitoring calls will occur weekly. If GVHD is identified, relatedness and attribution will be discussed by Investigator and monitoring committee will decide on further enrollment.

# 15 DATA HANDLING AND RECORD-KEEPING

## 15.1 ECRFs

Case report forms are presented in the appendix.

# 16 STATISTICAL CONSIDERATIONS

Study design/Sample size

This is a phase I/II study evaluating the combination of Daratumumab and escalating doses of DLI in patients with relapsed AML or transformed from MDS to AML post allo-HCT. Three dose levels will be used for related sibling donors and unrelated donors respectively.

Study Design: The standard 3+3 design will be applied to determine MTD of donor lymphocyte infusion when given with a fixed dose of Daratumumab. The dose escalation process for related sibling donor and unrelated donor will be conducted concurrently, but separately.

Dose escalation will proceed within each cohort according to the following scheme.

| Number of Subjects with DLT at a Given Dose Level | Escalation Decision Rule |
|---|---|
| 0 out of 3 | Enter 3 subjects at the next dose level. |
| 1 out of 3 | Enter 3 more subjects at this dose level.<br>• If 0 of these 3 subjects experience DLT, proceed to the next dose level.<br>• If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) |

| | |
|---|---|
| | additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose. |
| >2 | Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose. |
| <1 out of 6 at highest dose level below the maximally administered dose | This is generally the recommended maximally tolerated dose. |

The MTD will be defined as the highest safely tolerated dose where at most one patient in six experiences DLT during DLT observation period. The DLT observation period is defined as below.

| Dose Level | DLT observation period |
|---|---|
| 1 | From the first dose of Daratumumab till 7 days post 3rd dose |
| 2/3 | From the first dose of Daratumumab till at least 4 weeks post DLI |

If a patient in dose level 1 receives less than 3 doses of Daratumumab due to reasons other than toxicity, then this patient will not be evaluable for DLT and will be replaced. An additional patient will be added to the dose cohort. For dose level 2 or 3, if a patient does not receive 3 doses of Daratumumab and DLI due to reasons other than toxicity, then this patient will not be evaluable and will be replaced. There will be no intrapatient dose escalation. Phase I may involve as few as 3 patients (three at the starting dose level if $\geq 2$ DLTs are experienced) and a maximum of 18 patients will be treated, six at each of the 3 dose levels. We assume that 10% of the patients in this group will not be evaluable due to not finishing the DLT observation period. So we expect to accrue a minimum of 4 patients and a maximum of 20 patients.

At OSU, 125 patients with AML/MDS underwent allo-HSCT in 2012 and 2013. Among these, 32 patients relapsed. About 40% were from related donor and 60% from unrelated donor. So we expect to accrue approximately 6 patients for the related sibling donor cohort and 10 patients for the unrelated donor cohort per year. Hence, the minimum study duration for phase I would be about 8-10 months and the maximum study duration would be around 2.5-3.5 years (accounting for the DLT observation period) for related sibling donors and unrelated donors respectively.

After the MTD has been established, we will expand to Phase II trial. For phase II part, considering that patients receiving transplant from related sibling donor or unrelated donor with each treated at the corresponding MTD of Daratumumab plus DLI are expected to have similar profiles for response and toxicities, we will combine these 2 cohorts together in phase II stage. The null hypothesis is that combination of Daratumumab and DLI has a response rate of < 10% in patients with relapsed AML following allo-HSCT. The alternative hypothesis is that Daratumumab has a response rate of at least 30% in patients with relapsed AML following allo-HSCT. With a type 1 error (alpha): 0.05, and a type 2 error (beta = 1 – power): 0.20, the sample size would be 25 patients for Phase II. If the number of patients achieving ORR is 6 or more, then we reject the null hypothesis. We would include 3-6 patients from

phase I who are treated at MTD in phase II analysis. Assuming 10% of the patients would be not evaluable for efficacy, we would expect to enroll 25 patients in phase II. With approximately 16 patients per year, and the study duration for phase II would be around 2 years including the follow up period (6-months).

## 16.1 Study endpoints:

Primary endpoint for phase I:
MTD of combination of Daratumumab and donor lymphocyte infusion

Primary endpoint for phase II:
Overall response rate to Daratumumab and DLI in patients with post-HCT relapsed AML and MDS

Secondary endpoints for phase II:

- ORR in MRD positive patients and in patients with overt morphological relapse
- MRD conversion rates
- 6 month post-relapse progression-free survival
- 6 month post-relapse overall survival
- 3 month GVHD rate

## 16.2 Analysis methods:

Analysis datasets:

Efficacy sets: All evaluable patients will be included in the analysis of the primary endpoint. The term evaluable is defined as any eligible patient who receives at least one dose of Daratumumab, does not withdraw consent, and is evaluated for response week 8; patients who fail to have a week-8 assessment due to early progression, death or toxicity will also be considered evaluable for response and categorized as non-responders. Patients who fail to have a week-8 assessment for other reasons (e.g., refusal due to travel constraints) will be considered unevaluable and will not be included in the denominator when calculating ORR rate.

Safety sets: The safety analysis dataset will include all eligible patients who receive one dose of daratumumab.

The adverse events will be examined and worst grade adverse events will be recorded for each patient and summarized by type, severity, and attribution (if possible) using NCI CTCAE version 4 criteria. Tolerability of the regimen will be assessed by summarizing the number of patients who require dose modifications and/or dose delays. In addition, we will also capture the proportion of patients who go off treatment due to adverse events or even those who refuse further treatment for lesser toxicities that inhibit their willingness to continue participation on the trial. All patients who have received at least one dose of daratumumab will be evaluable for toxicity and tolerability.

The primary endpoint of phase II is to evaluate overall response rates (ORR) to the combination of Daratumumab and DLI. The ORR will be defined as complete remission (CR), complete remission with incomplete marrow recovery (CRi), partial remission (PR) and morphological leukemia free

state (MLFS). The proportion of patients achieving ORR among efficacy sets will be calculated and 95% confidence interval will be estimated. In addition, the ORR among patients who received at least 3 doses of Daratumumab and DLI will be calculated as well. The ORR rate among MRD positive patients and patients with overt morphological relapse will be estimated as well. The MRD conversion rate from MRD positive to MRD negative, and the 3-month GVHD rate (both grade II-IV and III-IV) will be similarly analyzed.

Demographical and clinical characteristics of study patients will be described using mean and standard deviation, median and range, or frequency and percent depending on the data type and distribution. Overall survival (OS) will be defined as the time from the first treatment of Daratumumab to death or last contact date if no death. Progression free survival (PFS) will be defined as the time from the first treatment of Daratumumab to the date of progression or death or last clinical assessment date if no progression or death. Kaplan-Meier curves will be generated to estimate OS/PFS at 6 months. The association between patient characteristics and OS/PFS will be evaluated in univariable Cox proportional hazard regression model.

To examine the rate of GVHD (both grade II-IV and III-IV), the event will be onset of GVHD and time to GVHD will be defined as the period of time from first treatment of Daratumumab to the onset of GVHD. Death and early relapse without GVHD will be competing risks. Cumulative incidence rate of GVHD at 3-month with 95% confidence intervals will be estimated from the cumulative incidence curves. Competing risk regression analysis will be conducted to estimate the association between patient characteristics and GVHD.

For pre/post-treatment comparisons in the correlative part of the study, a paired t-test will be applied. Two-tailed p values <0.05 will be considered statistically significant in all analyses.

## 16.3 SAFETY ANALYSIS

The investigator-study team will collectively discuss study conduct and accumulating safety and other data through teleconferences. In Phase 1, it is expected that these discussions will be scheduled to occur immediately following DLT window for the third patient of each cohort unless accrual to the study and the need for decisions regarding dose escalation or stage progression indicate the need for more frequent reviews. In Phase 2, it is expected that these discussions will occur every month to discuss study conduct and accumulating safety and efficacy data through teleconferences.

A status report about adverse events, accrual will be submitted every 6 months to the Data Safety monitoring committee at Ohio State University

Patients who have evidence of rapidly progressive disease after 4 doses of Daratumumab will come off trial.

# 17 QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a

prospectively approved deviation) from the inclusion or exclusion criteria. The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the IRB. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the sponsor or designee for any significant deviation from the protocol.

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# 19 Appendix

## AML Baseline History Form

## 17102_AML Baseline History Form

| | |
|---|---|
| **Date of AML Diagnosis?** | |
| **Type?** | **Option List Name:** *AML_DISEASE_FORMS* ; **Option List Items:** *Achieved , Adverse , Aplasia , Complete Remission w/ incomplete recovery (CRi) , Complete Response (CR) , Cytogenetic Complete Response (CRc) , Definitive , Disease Progression , Favorable , Indeterminate Cause , Intermediate I , Intermediate II , Less than 5% blasts , Molecular Complete Response (CRm) , Morphologic leukemia-free state , N/A , No , Not Achieved , Not Done , Not Evaluable , Partial Response (PR) , Possible , Probable , Refractory , Relapsed , Resistant Disease , Stable Disease (SD) , Treatment Failure , Unknown , Untreated , Yes* |
| **Secondary AML?** | **Option List Name:** *YES_NO* ; **Option List Items:** ** , No , Not Applicable , Unknown , Yes* |
| **7+3 Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If 7+3 Therapy Yes, specify date** | |
| **HiDAC Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If HiDAC Therapy Yes, please specify date** | |
| **If HiDAC Therapy Yes, how many cycles?** | |
| **Auto ACT Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If Auto ACT Therapy Yes, please specify date** | |
| **Allo SCT?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If Allo SCT Yes, how many?** | |
| **Decitabine Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If Decitabine Therapy Yes, please specify date** | |
| **XRT Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If XRT Therapy Yes, please specify date** | |
| **Hydrea Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If Hydrea Therapy Yes, please specify date** | |
| **5-azacitadine Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **If 5-azacitadine Therapy Yes, please specify date** | |
| **Other Therapy?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |
| **Total Number of Prior Regimens** | |

| | |
|---|---|
| **Additional Details of Prior AML Therapy** | |
| **Date of Last Chemo Dose (ANY)** | |
| **Date of Last SCT** | |
| **Date of Last DLI** | |
| **HCT-CI** | |
| **Baseline ECOG Performance Status** | **Option List Name:** *ECOG_PERFORMANCE* ; **Option List Items:** *0 - Fully active , 1 - Restricted , 2 - Ambulatory , 3 - Capable of limited selfcare , 4 - Completely disabled , 5 - Dead* |
| **Transfusion Dependent PRBCs?** | **Option List Name:** *YES_NO* ; **Option List Items:** **, No , Not Applicable , Unknown , Yes* |
| **Transfusion Dependent Platelets?** | **Option List Name:** *YES_NO* ; **Option List Items:** **, No , Not Applicable , Unknown , Yes* |
| **Neutropenic?** | **Option List Name:** *YES_NO* ; **Option List Items:** **, No , Not Applicable , Unknown , Yes* |
| **If Neutropenic Yes, please specify duration of neutropenia** | |
| **Relapsed: CR1 Duration** | **Notes:** *Time from documentation of 1st CR to 1st Relapse* |
| **Relapsed: Number of Inductions to Achive CR1** | |
| **Refractory:Number of Failed Inductions** | |
| **History of CNS Disease** | **Option List Name:** *YES_NO* ; **Option List Items:** **, No , Not Applicable , Unknown , Yes* |
| **History of Extramedullary Disease** | **Option List Name:** *YES_NO* ; **Option List Items:** **, No , Not Applicable , Unknown , Yes* |
| **EML: Site of Extramedullary Disease** | **Notes:** *Please type in site (i.e. skin, sinus)* |
| **ELN Genetic Group** | **Option List Name:** *ELN_GENETIC_GROUPS* ; **Option List Items:** *adverse , favorable , intermediate-I , intermediate-II* |
| **If ELN Genetic Group Favorable, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |
| **If ELN Genetic Group Intermediate-I, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |

| | |
|---|---|
| **If ELN Genetic Group Intermediate-II, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |
| **If ELN Genetic Group Adverse, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |
| **Prior MDS** | **Option List Name:** *YES_NO* ; **Option List Items:** ** , No , Not Applicable , Unknown , Yes* |
| **Prior MPN** | **Option List Name:** *YES_NO* ; **Option List Items:** ** , No , Not Applicable , Unknown , Yes* |
| **Cellularity** | |
| **Blast** | |
| **Karyotype** | |
| **Karyotype continued** | |
| **Were Baseline Correlatives Collected?** | **Option List Name:** *YES/NO* ; **Option List Items:** *No , Yes* |

## 17102_Bone Marrow Screening/D1 Form

| | |
|---|---|
| **Bone Marrow: Blasts (%)** | |
| **Bone Marrow: ELN Genetic Group** | **Option List Name:** *ELN_GENETIC_GROUPS* ; **Option List Items:** *adverse , favorable , intermediate-I , intermediate-II* |
| **If Bone Marrow: ELN Genetic Group Favorable, please select Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |
| **If Bone Marrow: ELN Genetic Group Intermediate-I, please select Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |
| **If Bone Marrow: ELN Genetic Group Intermediate-II, please select Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |
| **If Bone Marrow: ELN Genetic Group Adverse, please select Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* ; **Option List Items:** *-5 or del(5q) , -7; abnl(17p) , CBFB-MYH11 , Cytogenetic abnormalities not classified as favorable or adverse , DEK-NUP214 , MLL rearranged , MLLT3-MLL , Mutated CEBPA (normal karyotype) , Mutated NPM1 and FLT3-ITD (normal karyotype) , Mutated NPM1 without FLT3-ITD (normal karyotype) , RPN1-EVI1 , RUNX1-RUNX1T1 , Wild-type NPM1 and FLT3-ITD (normal karyotype) , Wild-type NPM1 without FLT3-ITD (normal karyotype) , complex karyotype , inv(16)(p13.1q22) , inv(3)(q21q26.2) , t(16;16)(p13.1;q22) , t(3;3)(q21;q26.2) , t(6;9)(p23;q34) , t(8;21)(q22;q22) , t(9;11)(p22;q23) , t(v;11)(v;q23)* |
| **Is patient on antibiotics at time treatment started?** | **Option List Name:** *YES_NO* ; **Option List Items:** ** , No , Not Applicable , Unknown , Yes* |

## Concomitant Medications — CM: THX-CTMS-REV.03A

| Row # | 1. Start Date | 2. Stop Date | 3. Agent or Procedure | 4. Item | 5. Schedule | 6. Dose | 7. Dose Units | 8. Reason |
|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |

**Section Instructions**

| | |
|---|---|
| **Start Date** | |
| **Stop Date** | |
| **Agent or Procedure** | |
| **Item** | |
| **Schedule** | |
| **Dose** | |
| **Dose Units** | **Option List Name:** *UOM* ; **Option List Items:** *1000/mm3 , AUC , Centigrade , Drop(s) , Fahrenheit , Gy , IU , IU/mL , K/uL , MIU , MPFU , MU , MU/m2 , Sliding Scale , TCID , Tablet , U , U/l , U/l , U/ml , application , cGy , cells/mcL , cells/mm3 , cm , count/min , cubic centimeters , days , ft , g , g/24 hr , g/dl , g/m*m , gm , hours , in , kg , kilometers , l/sec , lb , m0sm/kg , m2 , mEq , mEq/24 hr , mEq/l , mL , mL/hr , mcg , mcg/kg , mcg/ml ...* |
| **Reason** | |

## Physical Exam — PE: THX-CTMS-REV.03A

**Section Instructions**

| | |
|---|---|
| **Examination Date** | |

| Row # | Body System | Finding | Comment If Any Change From Baseline |
|---|---|---|---|
| 1 | Abdomen | | |
| 2 | Breasts | | |
| 3 | Cardiovascular | | |
| 4 | Dermatologic | | |
| 5 | Endocrine/Metabolic | | |
| 6 | Gastrointestinal | | |
| 7 | Genitalia | | |
| 8 | H/E/E/N/T | | |
| 9 | Hematopoietic/Lymph | | |
| 10 | Immune | | |
| 11 | Musculoskeletal | | |
| 12 | Neck | | |
| 13 | Neurologic | | |
| 14 | Other | | |
| 15 | Pelvis | | |
| 16 | Psychologic | | |
| 17 | Respiratory | | |
| 18 | Urinary | | |

## Baseline Symptoms — BS: THX-CTMS-REV.03A

| Row # | 1. Onset Date | 2. Symptom Description | 3. Toxicity Code | 4. Grade | 5. Related to Disease? |
|---|---|---|---|---|---|
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |

## GVHD assessment at baseline

| | Acute GVHD | Chronic GVHD |
|---|---|---|
| Current state | Currently active - Yes or No | Currently active - Yes or No |
| Grade | Current grade | Current grade |
| Grade | Maximal grade | Maximal grade |
| Prednisone | Yes or No, dose if yes | Yes or No, dose if yes |
| Other immunosuppression | Yes or No | Yes or No |

## Vital Signs FA-PL: THX-CTMS-REV.03A

| Exam Name | Value |
|---|---|
| Diastolic BP | |
| Height (cm) | |
| Performance Status | |
| Pulse | |
| Pulse Ox (%) | |
| Respiration Rate | |
| Systolic BP | |
| Temperature (C) | |
| Weight (kg) | |

## Adverse Events TX: THX-CTMS-REV.03A

| No. | Start date of protocol | Adverse event description | Toxicity type | Onset date | Resolution of event | Grade | Time of event relative | Attribution Specify relation to | Dose-limiting toxicity | Action | Therapy | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **( AE or SAE)** | | **of event** | | | **to treatment plan?** | **disease Daratumumab, Transplant, DLI** | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

## EKG Form EKG_Form

| | |
|---|---|
| **EKG/ECG** | **Option List Name:** *NOR_ABNOR_NOTEXAM* ; **Option List Items:** *Abnormal , Normal , Not Examined* |
| **Comments** | |

## Hematology

## FA-HM: THX-CTMS-REV.03A

| Exam Name | Value |
|---|---|
| Hematocrit | |
| Hemoglobin | |
| INR | |
| Lymphocytes, Abs | |
| MCHC | |
| MCV | |
| Monocytes, Abs | |
| Neutrophils, % | |
| PT | |
| PTT | |
| Platelets | |
| RBC | |
| Red Cell Distribution Width (RDW) | |
| WBC | |
| WBC Bands | |
| WBC Basophils | |
| WBC Blast Cells | |

## Hematology, cont.

## FA-HM: THX-CTMS-REV.03A

| | |
|---|---|
| WBC Eosinophils | |
| WBC Lymphocytes | |
| WBC Monocytes | |
| WBC Neutrophils | |
| WBC Other - Diff. | |

## Blood Chemistries

## FB-BC: THX-CTMS-REV.03A

| Exam Name | Value |
|---|---|
| Albumin | |
| Alkaline Phosphatase | |
| Alkaline Phosphate | |
| Amylase | |
| BUN | |
| Bicarbonate | |
| Bilirubin (conjugated) | |
| Bilirubin (total) | |
| Blood Glucose - Fasting | |
| Blood Glucose - Non Fasting | |

## Blood Chemistries, cont.

## FB-BC: THX-CTMS-REV.03A

| | |
|---|---|
| Calcium | |
| Chloride | |
| Cholesterol | |
| Creatinine | |
| Creatinine Phosphokinase (CPK) | |
| Globulin (g/dl) | |
| Inorganic Phosphorus | |
| LDH | |
| Lipase | |
| Magnesium | |
| Potassium | |
| SGGT | |
| SGOT (AST) | |
| SGPT (ALT) | |
| Sodium | |
| Total Protein | |
| Triglycerides | |
| Uric Acid | |

**Serology** **FC-SR: THX-CTMS-REV.03A**

| Exam Name | Value |
|---|---|
| Pregnancy (code 0=negative, 1=positive) | |

## DLI Cell Infusion DLI_Cell_Infusion

| | |
|---|---|
| **Collection Date** | |
| **Start Time** | |
| **End Time** | |
| **Amount Collected (x10 8/kg)** | |
| **Date of Infusion** | |
| **Weight** | |
| **Amount Infused (x10 8/kg)** | |

## Drug Administration DA: THX-CTMS-REV.03A

| | |
|---|---|
| Start date and time | |
| Cycle and dose number | |
| Drug | |
| Lot number | |
| Dose level | |
| Route | |
| Duration | |

## 17102_AML On Treatment

17102_AML_On_Treatment

| | |
|---|---|
| Date of Hospital Admission | |
| Date of Hospital Discharge | |
| Number of days of GCSF | |
| Received ESA? | Option List Name: *YES_NO* ; Option List Items: **, No , Not Applicable , Unknown , Yes* |
| Number of PRBC units | |
| Number of platelet units | |
| Demonstrated refractoriness to platelet transfusion? | Option List Name: *YES_NO* ; Option List Items: **, No , Not Applicable , Unknown , Yes* |
| Does the patient currently have an infection? | Option List Name: *YES/NO* ; Option List Items: *No , Yes* |
| If current Infection Yes, please specify | Option List Name: *14040* ; Option List Items: *Bacterial , Controlled , Fungal , Uncontrolled , Viral* |
| If current Infection Yes, please specify type | Option List Name: *14040* ; Option List Items: *Bacterial , Controlled , Fungal , Uncontrolled , Viral* |
| Response | Option List Name: *AML_RESPONSE_CRITERIA* ; Option List Items: *Complete remission (CR) , CR with incomplete recovery (CRi) , Cytogenetic CR (CRc) , Death from indeterminate cause , Death in aplasia , Molecular CR (CRm) , Morphologic leukemia-free state , Not assessed , Partial remission (PR) , Relapse , Resistant disease (RD) , Stable Disease (SD)* |
| Treatment Failure? | Option List Name: *YES/NO* ; Option List Items: *No , Yes* |
| If Treatment Failure Yes, please specify | Option List Name: *AML_RESPONSE_CRITERIA* ; Option List Items: *Complete remission (CR) , CR with incomplete recovery (CRi) , Cytogenetic CR (CRc) , Death from indeterminate cause , Death in aplasia , Molecular CR (CRm) , Morphologic leukemia-free state , Not assessed , Partial remission (PR) , Relapse , Resistant disease (RD) , Stable Disease (SD)* |
| Was treatment plan interrupted? | Option List Name: *YES/NO* ; Option List Items: *No , Yes* |
| If treatment plan interrupted Yes, please explain | |
| Was dose modified? | Option List Name: *YES/NO* ; Option List Items: *No , Yes* |
| If dose modified Yes, please explain | |
| Other details | |

## 17102 AML Response Form 17102_AML_Response_Form

| | |
|---|---|
| **Date of First Day of Treatment** | |
| **Date of Response Assessment** | |
| **Therapy Day of Response Assessment** | **Notes:** *i.e. Day 35* |
| **Response** | **Notes:** *Please refer to protocol for specific definitions*<br>**Option List Name:** *AML_RESPONSE_CRITERIA* |
| **Treatment Failure?** | **Option List Name:** *YES_NO* |
| **If Treatment Failure, what kind?** | **Option List Name:** *AML_RESPONSE_CRITERIA* |
| **WBC** | |
| **ANC** | |
| **Platelets** | |
| **Blast %** | |
| **ANC Count > 500 K/uL** | **Option List Name:** *YES/NO* |
| **Date of ANC >500 K/uL** | |
| **Platelet Count > 50 K/uL** | **Option List Name:** *YES/NO* |
| **Date Platelet Counts > 50 K/uL** | |
| **Platelet Count > 100 K/uL** | **Option List Name:** *YES/NO* |
| **Date Platelet count > 100 K/uL** | |
| **Has patient achieved RBC transfusion independence?** | **Option List Name:** *YES/NO* |
| **If RBC transfusion independence Yes, specify date** | |
| **Has patient achieved platelet transfusion independence?** | **Option List Name:** *YES/NO* |
| **If platelet transfusion independence Yes, specify date** | |
| **Karyotype** | |
| **Cellularity %** | |
| **Blast %** | |
| **ELN Genetic Group** | **Option List Name:** *ELN_GENETIC_GROUPS* |
| **If ELN Genetic Group Favorable, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* |
| **If ELN Genetic Group Intermediate-I, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* |
| **If ELN Genetic Group Intermediate-II, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* |
| **If ELN Genetic Group Adverse, please specify Genetic Subset** | **Option List Name:** *ELN_GENETIC_SUBSETS* |
| **AML Response Comments** | |