MD Anderson IND Sponsor Cover Sheet

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Protocol Title	An Open-label, Phase 2 Trial Evaluating the Efficacy and Safety of Daratumumab in Combination with Venetoclax in Subjects with Relapsed/Refractory Acute Myelogenous Leukemia, High-Risk Myelodysplastic Syndrome or T Acute Lymphoblastic Leukemia/Lymphoma
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An Open-label, Phase 2 Trial Evaluating the Efficacy and Safety of Daratumumab in Combination with Venetoclax in Subjects with Relapsed/Refractory Acute Myelogenous Leukemia, High-Risk Myelodysplastic Syndrome or T Acute Lymphoblastic Leukemia/Lymphoma

Short title:	Daratumumab and venetoclax in AML/MDS
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1. Background

Acute Myelogenous Leukemia (AML) and High-Risk Myelodysplastic Syndrome (HR-MDS)

Long term outcomes in acute myeloid leukemia (AML) remain uniformly poor except in few cytogenetically and molecularly favorable subcategories.[1, 2] Despite progress in the understanding of leukemia pathophysiology, 20-40% of patients do not achieve remission with the standard induction chemotherapy and 50-70% of first complete remission patients are expected to relapse within 3 years.[3] The prognosis following AML relapse remains uniformly poor. High dose cytarabine (Ara-C) based therapy has been the cornerstone of salvage chemotherapy for relapsed or refractory AML for many years. The complete response rate in first salvage is approximately 30-50%. Addition of other cytotoxic agents such as mitoxantrone or etoposide has not improved complete response rates but may be associated with increased toxicities. Regimens incorporating clofarabine or cladribine with or without high dose Ara-C (HDAC) may improve remission rates but have not resulted in survival benefit.[4-6]

The same is true for patients with high risk myelodysplastic syndrome (HR-MDS). Front-line treatment with hypomethylating agents improves survival[7] but relapse of disease is the norm and survival among patients with relapsed HR-MDS is abysmally poor.[8]

Genomic sequencing has improved our understanding of ‘primary or driver’ mutations as well as ‘secondary or cooperating’ mutations in AML and MDS. These studies have also revealed clonal complexity of these diseases with existence of multiple clones with variety of mutations.[9] While targeting ‘driver’ mutations is an attractive strategy, the complex landscape of interacting mutations makes it difficult to envisage a strategy exclusively based on targeting mutations alone to be successful. Clinically this is supported by the fact that responses with kinase inhibitors targeting FLT3, MEK etc. are generally short lasting.[10] On the other hand 20-30% of patients with AML get cured of disease with chemotherapy based approaches (nucleoside analog and anthracycline based). Thus rational potentiation of chemotherapy effect on leukemia cells holds a promise of improving long term outcome in AML and MDS and not being restricted by presence of mutational events. Treatment directed against antigens expressed in leukemia cells offer such a mutation agnostic target.

CD 38 as target in AML therapy

Conventional perception is that the leukemia initiating cell resides in the CD34+/38- fraction of cells. However the phenotype of LIC is more heterogeneous as shown in the study of LIC in NPM1 mutated AML that is associated with low CD34 expression.[11] In this study many of the LICs resided within the CD34-/38+ population. Similarly in progression from chronic myelomonocytic leukemia (CMML) to AML, there is substantial expansion of the Lin-/CD34+/CD38+ progenitor cell population.[12] This population is highly proliferative, resistant to apoptosis and has

enhanced myeloid colony formation/replating ability. Thus targeting CD 38 is a viable therapeutic option in myeloid malignancies.

T Acute Lymphoblastic Leukemia/Lymphoma (T-ALL, T-LBL)
In T-cell ALL and T-cell LBL, the neoplasm is characterized by malignant expansion of immature lymphoblasts committed to the T-cell lineage. T-ALL and T-LBL are widely thought of as the same disease type differing only by the amount of involvement in the bone marrow. Infiltration above 25% is considered T-ALL and below 25% is T-LBL[13]. They are a heterogeneous group of diseases with regard to immunophenotyping, cytogenetics molecular genetic abnormalities, and clinical features including response to therapy.

Although ALL is relatively more common in children, it can also affect adults. T-ALL and T-LBL account for approximately 12% to 15% of childhood and 25% of adult ALL cases. Molecular subtypes of T-ALL with Notch mutations are found in about 50% to 60% of children and adults with T-ALL [13, 14].

Treatment for T-LBL has moved from traditional lymphoma protocols to treatments designed for ALL[13]. Treatment results in newly diagnosed adult patients with ALL have improved in the past decade with an increase of complete remission (CR) rates to between 85% and 90% and overall survival (OS) rates to between 40% and 50% with the developments of intensified and targeted chemotherapies and stem cell transplantation (SCT)[13]. The 5-year overall survival of T-ALL has improved to between 48% and 56%[15, 16]. T-ALL represents one of the most favorable subgroups of adult ALL. Mortality rates of T-ALL patients have significantly decreased over the last decades because of advances in the treatment of this aggressive subset of ALL. The 5-year OS rates are approximately 35% to 40% in adults and 75% to 85% for children and adolescents[17]. Despite the progress in the treatment results of newly diagnosed T-ALL or T-LBL, approximately half of these patients relapse within the first 2 years or fail to achieve a CR and have an extremely poor prognosis.

Response rates of 50% are achievable among relapsed or refractory T-ALL/T-LBL patients treated with high or intermediate doses of cytarabine-based combination therapy, but remissions are of short duration.

Response rates of 50% are achievable among relapsed or refractory T-ALL/T-LBL patients treated with high or intermediate doses of cytarabine-based combination therapy, but remission. Given the historically poor clinical outcomes for the majority of patients with relapsed T-ALL/T-LBL, there is a clear need for new treatment options.

CD38 as target in T-acute lymphoblastic leukemia/lymphoma
In a study from Children’s Hospital of Philadelphia, CD 38 expression was confirmed by flowcytometry in all T-ALL/LBL samples including those of early T-cell precursor ALL.[18] In that study the investigators report that daratumumab monotherapy was

effective in patient-derived xeneograft models developed from 14 of 15 patients with T-ALL.

Daratumumab
Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is currently approved for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. The drug is not approved for the indication being studied, AML and HR-MDS. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as multiple myeloma, lymphoma and B- and T-cell ALL and potentially subsets of AML. Daratumumab has multiple mechanisms of action (MoA), including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Importantly, daratumumab-induced ADCC and CDC do not appear to be affected by the presence of bone marrow stromal cells, indicating that daratumumab can effectively induce the killing of malignant cells in a tumor-preserving bone marrow microenvironment. In vivo studies have shown that daratumumab is highly active and interrupts xenograft tumor growth at low doses.[19]

Clinical Study Summary
In humans, daratumumab is tolerated well. Maximum tolerated dose (MTD) has not been reached following intravenous (IV) infusions up to 24 mg/kg monotherapy and 16 mg/kg in combination studies. The most frequently reported adverse events (AEs) across the daratumumab program have been infusion-related reactions (IRRs) following single agent therapy. Among all subjects treated in ongoing studies (monotherapy and combination therapy), IRRs have been reported in 49% of subjects. (Reference: Appendix G, Investigator's Brochure).

Daratumumab will be provided at no cost to the patient.

Venetoclax
Venetoclax (Venclexta™) is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Venetoclax is approved for treatment of chronic lymphocytic leukemia (CLL) and in combination with azacitidine, decitabine or low-dose cytarabine to treat older adults with AML. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases.

In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2. Pre-clinical studies in T-ALL, particularly a high-risk subtype of early T-cell precursor acute lymphoblastic leukemia (ETP-ALL), using BH3 profiling, have revealed BCL-2 dependence with exquisite in vitro sensitivity to

the BCL-2–selective antagonist venetoclax.[20, 21]. Limited clinical experience also suggests that venetoclax is active against T-ALL.[22]

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 µM (0.87-26 µg/mL). The population estimate for the terminal elimination half-life of venetoclax was approximately 26 hours. The pharmacokinetics of venetoclax does not change over time.

Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated. Concomitant use of venetoclax with strong CYP3A inhibitors increases venetoclax exposure (i.e., Cmax and AUC) and may increase the risk for tumor lysis syndrome at initiation and during ramp-up phase. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when strong CYP3A inhibitors must be used concomitantly.

Concomitant use of venetoclax with moderate CYP3A inhibitors or P-gp inhibitors should be avoided. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the venetoclax dose by at least 50%. These patients will be monitored more closely for signs of toxicities and will resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

2. **Venetoclax will be obtained from commercial source and is the responsibility of the patient and/or insurance company.** **Study Population**

Patients with relapsed/refractory acute myelogenous leukemia, high-risk myelodysplastic syndrome, or relapsed/refractory T-ALL/T-LBL.

3. Study Objectives

Primary Objectives

The primary objective of this study is to assess response rate as determined by the International Working Group recommendations in AML, MDS[23, 24] and in adult patients with relapsed/refractory T-ALL/T-LBL.

Secondary Objectives

The secondary objectives of this study are to assess:

- Safety and tolerability
- Time on treatment
- Overall survival
- Progression free survival

- Long-term response rate

Exploratory Objective
To explore biomarkers predictive of response or resistance to therapy including expression of CD38 at study entry and at relapse and response rate based on CD38 expression level.

4. Hypothesis

For relapsed/refractory AML/high risk MDS and relapsed/refractory T-ALL/T-LBL, the primary hypothesis is that daratumumab in combination with venetoclax will improve the overall response rate from the historical rate of 15% by at least 10% (i.e., 25% response rate).

5. Study Design

This is a single center, Phase 2, open-label study of daratumumab and venetoclax in subjects with relapsed/refractory AML, high risk MDS and relapsed/refractory T-ALL/T-LBL. Subjects in a cohort of 6 with up to 36 subjects will be enrolled to receive daratumumab and venetoclax. Each cycle will be 4 weeks (28 days). Daratumumab will be administered at 16mg/kg weekly for the first 2 cycles (8 weeks) of treatment, followed by every 2 weeks for 4 cycles (or 16 weeks) weeks and then every 4 weeks until progression or up to 1 year of treatment whichever comes earlier. Venetoclax administration will follow the schedule indicated in package insert for administration in AML. (www.rxabbvie.com/pdf/venclexta.pdf) Venetoclax will be administered for 21 days in each cycle and clinician will use appropriate judgement about number of days of venetoclax beyond cycle 1, based on disease status and blood counts. Tumor lysis syndrome (TLS) prophylaxis during dose ramp-up of venetoclax will be per label of venetoclax for use in AML.

On days of daratumumab dosing, the subject will receive pre-infusion medications and on the 2 days after receiving daratumumab dosing, the subject will receive post-infusion corticosteroid prophylaxis for IRR. See **Section 7C and D**.

MDACC Investigational New Drug (IND) office will review interim safety data with Principal Investigator (and statistician if needed) at a predetermined interim safety analyses interval as indicated next. The first analysis will occur after the first 6 subjects are treated for at least 1 cycle. Enrollment will be temporarily halted after first six subjects have been enrolled and treated. If deemed safe, enrollment will resume and safety monitoring will be conducted in cohort size of 6 thereafter, as detailed in the Statistical Considerations section. We will also implement a Bayesian futility monitoring for overall response rate in cohort size of 6. However, enrollment will not need to be held. As enrollment is expected to be at 1-2 patients a month this would not substantially impact futility monitoring.

6. Eligibility Criteria

A. Inclusion criteria:

1. Understand and voluntarily sign an informed consent form.
2. Age >/=18 years at the time of signing the informed consent form.
3. Diagnosis of AML [other than acute promyelocytic leukemia (APL)] with refractory/relapsed disease; patients with relapsed/refractory high-risk [(intermediate-2 or higher by International Prognostic Scoring System (IPSS) and/or >/= 10% blasts)] MDS will also be eligible. (Treatment approach for relapsed/refractory AML is very similar to that of high risk MDS), or diagnosis of relapsed/refractory T-ALL/T-LBL.
4. All non-hematological toxicity of previous cancer therapy should have resolved to </= grade1 (except alopecia or other toxicities not involving major organs).
5. Eastern Cooperative Oncology Group (ECOG) performance status of </= 2 at study entry.
6. Laboratory test results within these ranges:
   - Serum creatinine </= 2 mg/dL and estimated glomerular filtration rate or creatinine clearance >/= 40 ml/min
   - Total bilirubin </= 2 mg/dL
   - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) </=3 x upper limit of normal (ULN)
7. Women of childbearing potential must be practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/ cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject) during and after the study (3 months after the last dose of daratumumab for women).
8. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.
9. AML relapse > 6 months since autologous or allogeneic stem cell transplantation, provided there is no active graft-versus-host disease (GVHD) > grade 1; no treatment with high dose steroids for GVHD (up to 20 mg Prednisolone or equivalent); no treatment with immunosuppressive drugs with the exception of low dose cyclosporine and tacrolimus (blood levels of 0.5-0.6 µg/mL).

B. Exclusion Criteria:

1. White blood cell count more than 25 × 10^9 /L prior to initiation of venetoclax.
2. Pregnant or breast feeding females.
3. Cancer chemotherapy within 2 weeks prior to start of daratumumab treatment (exception hydroxyurea). Use of hydroxyurea to control proliferative disease will be allowed prior to starting therapy on study and for 7 days during cycle 1-3 (Maximum daily dose of 7gm).
4. Subject has received daratumumab or other anti-CD38 therapies previously.
5. Subject has received a cumulative dose of corticosteroids more than the equivalent of >/= 140 mg of prednisone within the 2 week period before Cycle 1, Day 1.
6. Subject has known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. **NOTE**: FEV1 testing is required for patients suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.
7. Subject has a history of another malignancy within 5 years before Cycle 1, Day 1 (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the IND office and supporter's medical monitor, is considered cured with minimal risk of recurrence).
8. Subject is known to be 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.
9. Subjects who are 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) will be excluded.
10. Subject has clinically significant cardiac disease, including:
    - myocardial infarction within 1 year before Cycle 1, Day 1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV)
    - Cardiac arrhythmia (CTCAE Version 4.03 Grade 2 or higher) or clinically significant ECG abnormalities.
    - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec.
11. Subject has known severe allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, or their excipients (refer to the

latest version of the Investigator Brochure), or known sensitivity to mammalian-derived products.

12. Subject has any concurrent medical condition or disease (e.g., active systemic infection, laboratory abnormalities) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.
13. Exclude patients with known Kell antibodies.

7. Dosage and Administration

Daratumumab will be administered at 16mg/kg for the first 2 Cycles (one time per week for 8 weeks) of treatment, followed by every 2 weeks for 4 cycles (or 16 weeks) and then every 4 weeks until progression or up to 1 year whichever comes earlier. All cycles are 4 weeks (28 days). The first visit of a cycle should be 4 weeks (+/- 3 days) after the start of the previous cycle, except in case of toxicities, see **Section 7B**. Every effort should be made to keep subjects on the planned dosing schedule.

Preparation

Infusion solution will be prepared as a 1000 mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump (**Table 2**). The study drug must be filtered by using an inline filter (0.2 µM) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to pharmacy.

Venetoclax administration will follow following schedule for Cycle 1:

Table 1: Venetoclax dosing guidelines

	Day 1	Day2	Day3	Day 4-21
Not on mod/strong CYP inhibitor or Pgp inhibitor	100 mg	200 mg	400 mg	400 mg
On moderate CYP inhibitor or Pgp inhibitor	50 mg	100 mg	200 mg	200 mg
On strong CYP inhibitor excluding posaconazole	10 mg	20 mg	50 mg	100 mg

Receiving posaconazole	10 mg	20 mg	50 mg	70 mg

For Cycle 2 onwards venetoclax will be dosed on days 1-21 at the dose intended to be administered on days 4-21 in cycle 1, but will start at that dose from Day1. Clinical judgement will be used to reduce the number of days of venetoclax administration based on disease status, ongoing clinically relevant issues e.g. infection, renal dysfunction etc.

Tumor lysis syndrome (TLS) prophylaxis during dose ramp-up of venetoclax will be per label of venetoclax for use in AML.

A. Treatment Schedule and Administration (Daratumumab)

Daratumumab will be administered as an intravenous (IV) infusion (**Table 2**). Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study, unless the patient's weight changes more than 10% from baseline. All infusions will be planned as outpatient visits. If needed, infusion can be done in the in-patient setting. Subjects will receive pre-infusion medications and post-infusion medications as detailed in **Sections 7C and D.**

Table 2. Infusion rates for daratumumab administration

	Dilution volume	Initial rate (first hour)	Rate increment	Maximum rate
First infusion	1000 ml	50ml/hr	50 ml/hr every hr	200 ml/hr
Second infusion[a]	500 ml	50 ml/hr	50 ml/hr every hr	200 ml/hr
Subsequent infusion[b]	500 ml	100 ml/hr	50 ml/hr every hr	200 ml/hr

a. Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.
b. Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥ 100 mL/hr in the first two infusions.

Daratumumab will be administered as noted below:

- Cycles 1 and 2: One time per week on Days 1, 8, 15, and 22. On Days 8, 15, and 22 (+1 day window).
- Cycle 3 to 6: Once every 2 weeks, Days 1 and 15 (+/- 3 days).
- Cycles 7+: Once every 4 weeks, Day 1 (+/- 7 days).

These windows will be used for delays not related to toxicities. For delays caused by toxicities please refer to **Table 3**.

For additional details for administration times and rates please refer to **Table 2** and Daratumumab package insert (https://www.janssenmd.com/pdf/darzalex/DARZALEX_PI.pdf).

All subjects should have vital signs monitored at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

B. Dose Delays and Dose Modification

a. Daratumumab

Dose Modification

No daratumumab dose modification (increase or decrease) will be permitted.

Toxicity Management

ONLY if any of the following criteria are met and the event is considered related to daratumumab then the next scheduled daratumumab infusion must be held to allow for recovery from toxicity.

The criteria for a dose delay are as follows:

Grade 3 or higher non-hematologic toxicities with the following exceptions:

- Grade 3 nausea that responds to antiemetic treatment within 7 days
- Grade 3 vomiting that responds to antiemetic treatment within 7 days
- Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
- Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
- Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab
- isolated Grade 3 or higher glutamyltransferase elevation

If daratumumab administration does not commence within the prespecified window (**Table 3**) of the scheduled administration date (either for toxicity or extenuating circumstances), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 3. Daratumumab-related Toxicity Management

Cycles	Frequency	Dose Miss	Dosing Resumption
1 -2	Weekly (Q1W)	>3 days	next planned weekly dosing date

3-6	Every 2 weeks (Q2W)	>7 days	next planned every 2 weeks dosing date
7+	Every 4 weeks (Q4W)	>14 days	next planned every 4 weeks dosing date

A missed dose will not be made up. **If a dose is delayed (beyond the usual permissible window), then the dates of all subsequent doses must be adjusted.** Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab.

Interruption or Missed Doses

Subjects missing >/= 3 consecutive planned doses of daratumumab for toxicity related to daratumumab should be withdrawn from the study. For subjects missing >/= 3 consecutive planned doses of daratumumab with reasons other than toxicity should also be withdrawn, unless upon consultation with the IND office and review of the safety and efficacy, continuation is agreed upon.

b. Venetoclax:

Venetoclax dose reduction will follow its dose modification suggestions in acute myeloid leukemia from its package insert.

Additional dose reductions and delays are allowed for venetoclax in cycle 1 and subsequent cycles if considered in the best interest of the patient and based on expertise of the investigator.

C. Pre-infusion medication (Daratumumab)

Administer pre-infusion medications to reduce the risk of infusion reactions to all patients approximately 1 hour prior to every infusion of daratumumab as follows:

- intravenous corticosteroid (methylprednisolone 100 mg, or equivalent dose of an intermediate-acting or long-acting corticosteroid), plus
- oral anti-pyretics (acetaminophen 650 to 1000 mg), plus
- oral or intravenous antihistamine (diphenhydramine 25 to 50 mg or equivalent).

Following the second infusion, the dose of corticosteroid may be reduced (methylprednisolone 60 mg intravenously). Please refer to Appendix B: Corticosteroid Comparison Chart for conversion of steroid dose.

D. Post-infusion Medication (Daratumumab)

For the prevention of delayed infusion-related reactions (IRR), all subjects will receive corticosteroid orally (20 mg methylprednisolone or equivalent in

accordance with local standards). See Appendix B: Corticosteroid Comparison Chart on the 2 days following all daratumumab infusions (beginning the day after the infusion).

For subjects with a higher risk of respiratory complications (e.g., subjects who have an FEV1 <80%), the following post-infusion medications should be considered:

- H1-Antihistamine (diphenhydramine, cetirizine, or equivalent) on the first and second days after all infusions
- Short-acting β2 adrenergic receptor agonist such as albuterol aerosol at any time as medically indicated.
- Control medications for lung disease (e.g., inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with chronic obstructive pulmonary disease) as medically indicated. In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their spirometry test (FEV1) should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.

Any post-infusion medication will be administered after the infusion has completed, per the timing noted above.

E. Management of Infusion-related Reactions (Daratumumab)

Subjects should be carefully observed during daratumumab infusions (**Table 2** for infusion rates). Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time. If an infusion-related reaction develops, then the infusion should be paused. In case of an infusion-related reaction, maintain the vital sign time points in relation to the initial start of the infusion. Additional vital sign time points are to be performed at the discretion of the investigator. Only clinically significant findings

need to be reported on unscheduled case report forms. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines apply:

- Subjects should be treated with acetaminophen, H1-antihistamine, or corticosteroids as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require H1-antihistamines, oxygen, corticosteroids, and/or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and after consultation with the supporter's and/or IND office's medical monitor, no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied. If an infusion is paused, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event.

Infusion-Related Reactions of Grade 1 or Grade 2

For infusion related adverse events that are Grade 1 or 2, the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be withdrawn from treatment.

Infusion-Related Reactions of Grade 3 or Higher

For infusion-related adverse events that are Grade 3 or higher, the infusion must be stopped and the subject must be observed carefully until resolution of the adverse event. If the intensity of any other adverse event remains at Grade 3 after 2 hours, then the subject must be withdrawn from treatment. Any patient with grade 4 infusion related reaction will also be withdrawn from treatment. If the intensity of any other adverse event decreases to Grade 1 or 2 within 2 hours, then the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the intensity of the adverse event returns to Grade 3 or 4 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then the subject must be withdrawn from treatment. Any patient with grade 4 infusion related reaction at any time will be withdrawn from treatment.

F. Permitted Therapies

Use of hydroxyurea to control proliferative disease will be allowed prior to starting therapy on study and for up to 7 days (per cycle) during Cycles 1-3 (maximum daily dose of 7gm). Use of growth factors (G-CSF, GM-CSF and erythrpoietic growth factors) will be permitted if considered to be in the best interest of the patient. Use of prophylactic/therapeutic antiemetics, antibiotics, antivirals and antifungals are permitted as per the decision of the treating physician. Prophylactic antiviral prophylaxis is recommended for all patients unless contraindicated.

G. Prohibited Therapies

Concomitant administration of investigational agents, including medications that target CD38, with the intention of treating AML/MDS are prohibited. Administration of commercially available agents with activity against or under investigation for AML/MDS/T-ALL (except hydroxyurea) should be avoided.

Concurrent use of corticosteroids is prohibited, unless used for prevention or treatment of infusion reactions (as above) or patients are on chronic steroids (maximum dose 20 mg/day prednisone equivalent) if they are being given for disorders other than treatment of AML/MDS, i.e., adrenal insufficiency, rheumatoid arthritis, etc.

H. Duration of Therapy

If a patient continues to respond or receive clinical benefit, he/she can continue treatment.

In the absence of treatment delays due to adverse event(s), treatment may continue once every four weeks (28 days) until one of the following criteria applies: disease progression or 1 year of treatment whichever is earlier.

8. Study Procedures

All study procedures are presented in **Table 7. Schedule of Study Events**. Results of all assessments will be recorded on the appropriate CRF. Study treatment should be initiated within 72 hours after registration. One cycle is 4 weeks (28 days) in duration. The start of each cycle may occur +/- 3 days of the scheduled day in order to accommodate the schedule of the site or subject.

Beyond day 1, safety laboratory evaluations can be done according to the time window provided for subsequent dosing.

i. Screening Procedures

The investigator will inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject

prior to performing any study-related procedures and prior to the administration of study drug.

The results of the screening evaluation must meet the inclusion/exclusion criteria for the subject to be entered into the study. Thus the investigator must review the results of diagnostic testing (bone marrow biopsy/aspirate and serum pregnancy test [if applicable], and clinical laboratory tests), and the results of that screening testing must meet the inclusion/exclusion criteria for the subject to be enrolled into the study.

ii. Daratumumab Interference with Indirect Antiglobulin Test (IAT) results

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient information card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. MDACC Blood bank will also be alerted when a subject is enrolled on study. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT).[25]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

- Providing ABO/RhD compatible, phenotypically or genotypically matched units
- Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab IB.

iii. Clinic Visits

The procedures for each visit are listed in **Table 7 Schedule of Study Events**.

A bone marrow aspirate and/or biopsy with differential and estimate of cellularity at baseline, on Day 1 (+/- 2 days) of each cycle after Cycle 1 until response is achieved. Subsequent bone marrow examinations will be performed at treating physician's discretion (suggested every 2-3 months).

D. Follow-up Period

Follow-Up procedures will occur after End of Treatment (EoT). The subject will be contacted regularly by telephone, approximately 1 time each month for the first year after the EoT visit, then every 6 months during the second year, and then 1 time each year after that to determine survival status. Any adverse events ongoing when subject stops the study will be followed by the Investigator until the event resolves, stabilizes, or returns to baseline status.

For the subject with response, the Follow-Up procedures include blood draw for CBC/Chemistry once per month for first 2 years after the EoT visit. Patients with continued response will be moved from this study to be followed under Leukemia Department umbrella protocols.

End of Treatment

At the time of discontinuation of treatment for any reason, subjects will report to the study site. EoT assessments may be performed at the discretion of the investigator. This assessment is to be completed 28-35 days after last dose administered.

9. Criteria for Response for Acute Leukemias and MDS

International Working Group Criteria[23, 24] will be used to define response. In general responses will include

1. Complete remission (CR): The patient must be free of all symptoms related to leukemia and have an absolute neutrophil count >/= 1.0 x 10^9/L, platelet count >/- 100 x 10^9/L, and normal bone marrow differential (</= 5% blasts).
2. Complete remission without platelet recovery (CRp): As per CR but platelet count < 100 x 10^9/L.
3. Partial remission (PR): CR with 6 to 25% abnormal cells in the marrow or 50% decrease in bone marrow blasts.
4. Marrow CR: Bone marrow: </= 5% myeloblasts and decrease by >/= 50% over pre-treatment (MDS only)
5. Morphologic leukemia-free state: Normal marrow differential (<5% blasts); absolute neutrophil count and platelet counts are not considered. (AML only)

6. Hematologic Improvement (HI): HI should be described by the number of individual, positively affected cell lines (e.g. HI-E; HI-E + HI-N; HI-E + HI-P +HI-N)
   a) Erythroid response (HI-E):
      - Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent subjects, transfusion independence.
      - Minor response: For patients with pretreatment hemoglobin less than 11 g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.
   b) Platelet response (HI-P):
      - Major response: For patients with a pretreatment platelet count less than 100 x 10^9/L, an absolute increase of 30 x 10^9/L or more; for platelet transfusion-dependent patients, stabilization of platelet transfusion independence.
      - Minor response: For patients with a pretreatment platelet count less than 100 x 10^9/L, a 50% or more increase in platelet count with a net increase greater than 10 x 10^9/L but less than 30 x 10^9/L.
   c) Neutrophil response (HI-N):
      - Major response: For absolute neutrophil count less than 1.5 x 10^9/L before therapy, at least a 100% increase, or an absolute increase of more than 0.5 x 10^9/L, whichever is greater.
      - Minor response: For ANC less than 1.5 x 10^9/L before therapy, ANC increase of at least 100%, but absolute increase less than 0.5 x 10^9/L.

10. Exploratory Studies

The baseline expression of CD38 in leukemic blasts will be assessed by flow cytometry. Expression of other marker of leukemia blasts will be available as part of routine clinical flow cytometry. This will include but not limited to CD33, 34 etc.

The mutation profile of leukemia relevant genes also will be available as part of routine work up done through Molecular Diagnostic Laboratory at MDACC.

11. Statistical Considerations

This is a Phase II study of daratumumab and venetoclax in patients with relapsed/refractory AML, high risk MDS and T-ALL/T-LBL. Subjects will enrolled in a cohort size of 6 with up to 36 to receive daratumumab and Venetoclax. The intent will be to enroll at least 10 patients with T-ALL. Daratumumab will be administered at a starting dose of 16mg/kg every week for 8 weeks (2 cycles), followed by 16mg/kg every 2 weeks for 16 weeks (4 cycles), and then every 4 weeks until progression or up to 1 year of treatment, whichever comes earlier. Venetoclax administration will follow its package insert dosing guidelines for AML. The primary endpoint of this study is overall response (OR), defined as achievement of complete remission (CR), CR with incomplete platelet recovery (CRp), partial remission (PR), morphologic leukemia-free

state or marrow CR within 12 weeks of treatment. The method of Thall, Simon and Estey[26] will be used to monitor efficacy and safety. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the stopping boundaries and the operating characteristics table for futility and toxicity monitoring.

Futility

We assume a target response rate of 25% and a response rate of 15% or lower will be considered not desirable. The study will be stopped early if the data suggest that:

$$Pr(P_E > P_H + 0.10 \mid data)<0.025$$

where P_E and P_H are the response rates for daratumumab in combination with venetoclax and historical treatment, respectively. That is, if at any time during the study we determine that there is less than 2.5% chance that the response rate improves over historical rate by more than 10%, the trial will be stopped due to futility. P_E and P_H are assumed to follow a prior of Beta (0.3, 1.7) and Beta (150, 850), respectively. The stopping boundaries for efficacy based on these assumptions and monitoring conditions are provided in **Table 4**. We will apply these stopping boundaries in cohort sizes of 6.

Table 4. Stopping boundaries for futility monitoring

# of patients evaluated for response	Stop the trial if # of patients with response is less than or equal to:
6-12	0
18	0-1
24	0-2
30	0-3
36	0-4

Toxicity

Unacceptable toxicities are defined as any treatment-related grade 3 or higher non-hematologic toxicities that occur within the first 12 weeks of treatment. Denote the probability of toxicity by P_T. We assume as a priori, P_T ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement:

$$Pr(P_T > 0.30 \mid data)>0.975.$$

That is, we will stop the trial for new patient enrollment if at any time during the study, we determine that there is more than 97.5% chance that the unacceptable toxicity rate is more than 30%. This toxicity monitoring rule will be applied after the first 6 patients have been enrolled and evaluated, and then in cohort size of 6. Stopping boundaries corresponding to this stopping rule are listed in **Table 5**. The operating characteristics for efficacy and toxicity monitoring are summarized in **Table 6**.

Table 5. Early stopping boundaries for toxicity monitoring

# of patients (in cohort size of 6, starting from the 6th patient)	Stop the trial if there are this many patients with toxicities:
6	5-6
12	8-12
18	10-18
24	13-24
30	15-30
36	17-36

Table 6. Operating characteristics for efficacy and toxicity monitoring

True response rate	True toxicity rate	Prob (stop the trial early)	Average number of patients treated
0.15	0.10	0.5752	25.3
	0.30	0.5959	24.7
	0.40	0.7049	22.3
	0.50	0.8895	17.3
0.25	0.10	0.2119	35.0
	0.30	0.2504	34.1
	0.40	0.4526	30.2
	0.50	0.7950	22.3
0.30	0.10	0.1282	37.6
	0.30	0.1708	36.6
	0.40	0.3945	32.3
	0.50	0.7732	23.6

Analysis Plan

Summary statistics will be provided for continuous variables and frequency tables will be used to summarize categorical variables. We will estimate the overall response rate, along with the Bayesian 95% credible interval. Kaplan-Meier method will be used to estimate overall survival, time to treatment and progression-free survival. The two-sided log-rank tests will be used to assess the differences of time-to-event outcomes between subgroups of patients. Logistic regression analyses will be used to explore the association between biomarker and response or resistance to therapy.

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study but did not take any of the study drug and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency.

12. Adverse Events and Reporting Requirements

Adverse event reporting will be as per the current NCI criteria and the Leukemia-specific Adverse Event Recording and Reporting Guidelines (Appendix D) . The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. http://ctep.cancer.gov/reporting/ctc.html

A. Adverse Events

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events, and assigning attribution for each event on all subjects enrolled on this study.

For this protocol, adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.

Only unexpected AEs related to the study drug will be recorded in the Case Report Form (CRF). Expected events during leukemia therapy are:

1. Myelosuppression related events (due to disease or leukemia therapy)

a) febrile or infection episodes not requiring management in the intensive care unit
b) epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage
c) anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis

2. Disease related events

a) symptoms associated with anemia
    i. fatigue
    ii. weakness
    iii. shortness of breath
b) electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)
c) chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)
d) coagulation abnormalities
e) disease specific therapy (induction, maintenance, salvage, or stem cell therapy)
f) alopecia

g) bone, joint, or muscle pain
h) liver function test abnormalities associated with infection or disease progression
i) disease progression

3. General therapy related events

a) catheter related events
b) renal failure related to tumor lysis syndrome or antibiotic/antifungal therapy
c) rash related to antibiotic use
d) abnormal hematologic values will not be recorded on the CRF. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

B. Serious Adverse Event (SAE) Reporting

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

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

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

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be**

reported as an SAE if deemed appropriate by the Principal Investigator or the IND Supporter, IND Office.

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

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

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

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

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

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

C. Reporting to FDA

- Serious adverse events will be forwarded to FDA by the IND Supporter (Safety Project Manager IND Office) according to 21 CFR 312.32.
- It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the supporter's guidelines, and Institutional Review Board policy.

13. Reporting SAE to Janssen Scientific Affairs, LLC

A. Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: DARZALEX™ (daratumumab)

B. Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs, LLC 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 (Only related to Daratumumab)
- Tumor Lysis Syndrome
- Other Malignancies
- Intravascular Hemolysis – All Grades

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.**

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 Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen 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)
- Janssen protocol ID

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., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

C. 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.

D. Special Reporting Situations

Safety events of interest for a Janssen 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 Janssen medicinal product

- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, 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 Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC 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 Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

E. Pregnancy

Females who choose to participate should not become pregnant during the study. Likewise, males participating in the study should not cause their partner to become pregnant while participating.

The effects of daratumumab and venetoclax on fertility, the human embryo, the fetus, or the breast-fed infant are unknown. Subjects must agree not to become pregnant while on this study. Subjects cannot take part in this study if they are pregnant or breastfeeding a child.

Women of childbearing potential will be required to undergo pregnancy tests prior to taking daratumumab and venetoclax. Males must not get anyone pregnant during the course of the study and for 3 months after stopping daratumumab and venetoclax.

Women must not donate eggs during the study and for 3 months after the last dose of study drugs.

Males must not donate sperm during the study and for 3 months after the last dose of study drugs.

Both male and female patients must use effective methods of birth control during the course of the study and for 3 months after stopping daratumumab and venetoclax.

The type of birth control used must be discussed with, and approved by, the study doctor before beginning the study. Approved birth control must be in the form of oral, injected or implanted methods (e.g., placement of an intrauterine device or intrauterine system, condom with spermicidal foam/gel/film/cream/suppository, diaphragm, cervical/vault caps with spermicidal foam/gel/film/cream/suppository, male partner sterilization, or abstinence).

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC 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 Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen 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.

F. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The 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 Janssen Scientific Affairs, LLC request.

G. Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs, LLC

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen 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 Janssen medicinal product.

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

H. SAEs, Adverse Events of Special Interest 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 PRINCIPAL INVESTIGATOR will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 11,Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC. 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 Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

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

The 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 correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in **Section 13L** within **24 hours of such report or correspondence being sent to applicable health authorities.**

I. Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

J. 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 Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC 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 Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen 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 Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

K. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen 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.

L. Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:

  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

The Investigator is obligated under applicable law and regulations to report any serious and related adverse event, if any that occurs during study treatment to the Institution's IRB/Ethics Committee and to the governing Regulatory Authority in accordance with applicable filing timelines promptly after any such event occurs. Prior to or at the time of filing any such report with the governing Regulatory Authority, the Investigator will also transmit an information copy of the report as sent to the authorities to Janssen. The Investigator shall make available to Janssen promptly such records as may be necessary and pertinent to investigate any such adverse event, if specifically requested by Janssen.

14. Drug Destruction Policy

Unused drug will be destroyed per Investigational Pharmacy "Return and Disposal of Investigational Medications."

15. References

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Table 7: Schedule of Study Events

	Notes	Screening Phase	Treatment (Cycles 1-2)	Treatment (Cycles 3-6)	Treatment (Cycles 7+)	EoT	Follow-up w/Response
		within 14 days	D1, D8, D15, D22	D1, D15	D1	(28-35 days after last dose)	(after EoT)
Procedures							
Informed consent	ICF must be signed before any study-related procedures are performed.	X					
Eligibility criteria		X					
Demography/ Medical History		X					
Height		X					
Weight	Dose of study medication does not need to be recalculated for weight changes <10%	X	D1 of each cycle[c]				
Spirometry / FEV1 test	For subjects with COPD or asthma, FEV1 should be measured[a]	X					
ECOG	See Appendix C	X	D1 of each cycle[c]				
12-lead ECG	Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) ≤470 msec	X		C3D1	C7D1	X	
Physical exam	Including neurological exam	X	Symptom and disease directed exam as clinically indicated				
Vital signs	Vital signs (blood pressure, heart rate, temperature) measured in sitting position. **On C1D1**: immediately before the start of daratumumab infusion; at 0.5, 1, 1.5, 2, 3.5 hr after start of infusion; at end of infusion; 0.5,1 hr after end of infusion.	X	X	X	X		

	Notes	Screening Phase	Treatment (Cycles 1-2)	Treatment (Cycles 3-6)	Treatment (Cycles 7+)	EoT	Follow-up w/Response
		within 14 days	D1, D8, D15, D22	D1, D15	D1	(28-35 days after last dose)	(after EoT)
	For all other infusions, vital signs measured immediately before start and at end of daratumumab infusion.						
Laboratory Assessments							
Serum Pregnancy test[b]	For women of childbearing potential only, within 14 days of first dose and again within 24 hrs of first dose.	X	X	Q4 Weeks			
Hematology	Includes WBC with differential, hemoglobin, platelet	X	X	X	X	X	X[*]
Serum Chemistry	Includes Na, K, Bicarbonate, BUN, creatinine, AST and/or ALT, Ca, Phosphorus, total bilirubin	X	D1, D15	D1	X	X	X
Bone Marrow aspirate and/or biopsy	Morphology, immunohistochemistry/ immuno fluorescence/flow cytometry as appropriate. With differential and estimate of cellularity.	X	C2, D1 (+/- 2 days)	C3, D1 every cycle until response (+/- 2 days) After that, according to investigator's discretion			
Blood type assessment and wallet card		X					
CMV screening		X	Every 2 weeks		Every 4 weeks		Every 4-12 weeks
HBV, HCV, HIV testing		X[e]					
HBV DNA testing			X[f]				
Ongoing Subject Review							
Adverse Events	See **Section 12** for detailed instructions		Continuous from the time of signing of ICF until 30 days after last dose of last study drug. Any adverse event ongoing at EoT will be followed until the event resolves, stabilizes or returns to baseline status.				
Concomitant Medications[d]			Continuous from the time of signing the ICF until 30 days after last dose of study drug.				

	Notes	Screening Phase	Treatment (Cycles 1-2)	Treatment (Cycles 3-6)	Treatment (Cycles 7+)	EoT	Follow-up w/Response
		within 14 days	D1, D8, D15, D22	D1, D15	D1	(28-35 days after last dose)	(after EoT)
Survival Status (no response)	Telephone interview lasting approximately 5 minutes: **Following EoT:** one time each month for the first year; every six months during the second year; one time per year thereafter						

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; C=cycle; Ca: calcium; CMV: PCR; COPD=chronic obstructive pulmonary disease; ECOG=Eastern Cooperative Oncology Group; D=day; ECG=electrocardiogram; EoT= End of Treatment; FEV1= Forced Expiratory Volume (in 1 second); HBV=surface antigen and core antibody; HCV: surface antigen and core antibody; HIV: 1/2; hrs: hours; ICF=informed consent form; K: potassium; Na: sodium; wbc: white blood cells

*Monthly for the first two years;
[a]See Appendix A. Classification of Asthma Severity
[b]Serum pregnancy test will occur at Screening (within 14 days) and Day 1 of each cycle prior to dosing. If screening pregnancy test occurs within 24 hours of first dose, it will not be repeated.
[c]Can be performed one day prior to D1 treatment
[d]Concomitant medications will be captured in the medical records except for hydroxyurea. Hydroxyurea will be captured in the medical record and case report form.
[e] Within 3 months from enrollment
[f] HBV DNA (Q12W during treatment, at EOT, and Q12W for up to 6 months 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