UCSF Helen Diller Family Comprehensive Cancer Center

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Phase II Study of Daratumumab in Combination with Azacitidine and Dexamethasone in Relapsed/Refractory Multiple Myeloma Patients Previously Treated with Daratumumab

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Protocol Signature Page

Protocol No.: 20251

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

UCSF Principal Investigator

Swetha Kambhampati, Alfred Chung

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Printed Name

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Signature Date

Abstract

Title	A Phase II Study of Daratumumab in Combination with Azacitidine and Dexamethasone in Relapsed/Refractory Multiple Myeloma Patients Previously Treated with Daratumumab
Study Description	This is a single-arm, 2-stage, phase II study of the safety and efficacy of daratumumab in combination with azacitidine and dexamethasone in relapsed/refractory multiple myeloma (RRMM) patients who have previously been exposed to daratumumab. Based on pre-clinical data we hypothesize that azacitidine, by upregulating the expression of CD38, can potentially increase the antibody-dependent cell-mediated cytotoxicity and efficacy of daratumumab on multiple myeloma cells and help reverse daratumumab resistance. This study aims to assess the efficacy and safety of daratumumab and azacitidine in relapsed refractory multiple myeloma.
Phase of Study	Phase 2
Investigational Products	Daratumumab and Azacitidine
Study population	Patients ≥ 18 years of age with relapsed or refractory multiple myeloma (RRMM) who have progressed on ≥ 2 lines of prior therapy, including an immunomodulatory drugs (IMiD) and proteasome inhibitor, and have previously been treated with daratumumab, with most recent daratumumab treatment being at least 6 months prior to enrollment to allow for CD38 normalization.
Primary Objective	• To evaluate the efficacy, as determined by the overall response rate (ORR) of daratumumab in combination with azacitidine and dexamethasone in RRMM patients who have previously been exposed to daratumumab
Secondary Objectives	• To evaluate duration of response per IMWG response criteria. • To assess the safety and toxicity of azacitidine in combination with daratumumab and dexamethasone • To assess the 1-year OS and PFS of daratumumab in combination with azacitidine and dexamethasone • To evaluate the change in CD38 expression on plasma cells induced by azacitidine in patients with RRMM and correlate this change with depth and duration of response

Sample Size	Simon's minimax two-stage design will be used. The overall study (including the safety lead-in) plans to enroll 23 patients. Safety Lead In: We expect to enroll 6 patients overall in the safety lead-in. Stage 1: We expect to enroll a total of 13 patients during Stage 1 (including the 6 patients enrolled in the safety lead-in). Depending on the clinical response in Stage 1, Stage 2 will commence. Stage 2: If there is ≥ 2 responses in 13 patients the study will enroll an additional 10 patients. If there is ≤ 1 response in 13 patients the study will be stopped.
Duration of Study Treatment	Participants will continue study treatment until they are unable to tolerate treatment due to toxicities or demonstrate progression. We anticipate the duration of study treatment to be around 8 months.
Duration of Follow up	Patients will be followed until 1 year after the last patient has received the last administration of daratumumab.
Unique Aspects of this Study	This is the first study to evaluate the safety and efficacy of azacitidine and daratumumab in combination with dexamethasone in patients with relapsed and refractory myeloma.

List of Abbreviations

ADCC	antibody-dependent cellular toxicity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
Aza	Azacitidine
BM	Bone marrow
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CDC	complement dependent cytotoxicity
CNS	central nervous system
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
Dara	Daratumumab
Dexamethasone	Dexamethasone
DFS	disease-free survival
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG/EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLC	free light chain
GCP	Good Clinical Practice

List of Abbreviations

GGT	gamma-glutamyl transferase
HBeAg	hepatitis B “e” antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
Mab/MoAb	Monoclonal Antibody
MFI	Median fluorescent intensity
MM	Multiple myeloma
MR	Minor response
MRI	Magnetic resonance imaging
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	disease progression
Pd	pharmacodynamics
PFS	progression free survival
PI	principal investigator
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
RRMM	Relapsed refractory multiple myeloma

List of Abbreviations

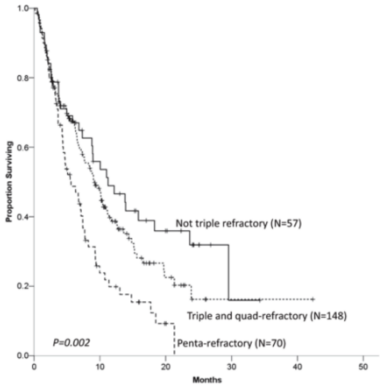
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
VGPR	very good partial response
WBC	white blood cell count

Table of Contents

1 Introduction

1.1 Background on Indication

In the last decade, the introduction of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) has significantly prolonged survival of patients with multiple myeloma (MM).[1,2] However, despite numerous advances in treatment, multiple myeloma is still considered an incurable disease with an overall 5-year survival rate of 51%.[3] Daratumumab , the first-in-class CD38 monoclonal antibody, has significantly improved the treatment response of MM, due to plasma cell overexpression of protein CD38.[4,5] Daratumumab binds CD38 with high affinity and induces tumor cell death through a variety of immune-mediated mechanisms of including complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).[6,7] Daratumumab monotherapy was approved for heavily pretreated relapsed refractory multiple myeloma (RRMM) patients[8] based on the open-label, phase I/II GEN501 study and phase II SIRIUS study which showed overall response rates of 36% and 29%.[9,10] Daratumumab, in the randomized open-label trials POLLUX and CASTOR, was also shown to have high response rates in RRMM when combined with Lenalidomide and Bortezomib, respectively, with a 63% and 61% risk reduction of disease progression or death.[11,12] More recently, trials such as ALCYONE[13] and MAIA[14] have lead to approval of front-line daratumumab combination therapies for untreated transplant-ineligible myeloma patients. ALCYONE showed that daratumumab, bortezomib, melphalan, and prednisone combination in this patient population had an overall response rate of 90.9% in the daratumumab group as opposed to 73.9% in the control group[13], while MAIA study showed that daratumumab, lenalidomide, and dexamethasone had a complete response of 47.6% in the daratumumab group as opposed to 24.9% in the control group[14]. Given the favorable results from the CASSOPEIA trial in Europe showing that daratumumab in combination with bortezomib, thalidomide, and dexamethasone (VTd), the frontline therapy standard of care in Europe in transplant eligible myeloma patients, resulted in 29% stringent complete response rate as opposed to 20% in the control non-daratumumab group[15]. There is an ongoing phase II GRIFFIN trial assessing the safety and efficacy of daratumumab in combination with revlimid, velcade, and dexamethasone (RVd) in frontline transplant eligible patients (NCT02874742). Preliminary data has indicated that this study has met its primary endpoint, demonstrating a higher percentage of stringent complete response (sCR) in patients in the daratumumab group compared to the control RVd group. While we are still awaiting the final results from this trial, if these preliminary results are confirmed in the final analysis, we anticipate daratumumab to be approved in the future in combination with the current standard of care RVd in frontline transplant-eligible myeloma patients. Now daratumumab is also approved in the subcutaneous form, based on the results of the COLUMBA study. The subcutaneous form provides several additional benefits for both patients and healthcare providers including shorter administration time, lower rate of infusion related reactions, additional flexibility, and reduction in treatment burden to the patient as well as lower risk of volume overload in patients with cardiac or renal insufficiency.



While daratumumab is well tolerated and has high efficacy, not all patients respond, and many patients eventually develop progressive disease and resistance to daratumumab. A retrospective study showed that these patients have poor prognosis with a median overall survival of 5.3 months and a post-daratumumab regimen overall response rate of 34% with limited treatment options.[16] Another retrospective study analyzing outcomes of 275 multiple myeloma patients at 14 academic centers with disease refractory to CD38 monoclonal antibodies (MoABs), either daratumumab or isatuximab, found that this patient population had a median overall survival (OS) of 8.6 months, ranging from 11.2 months for patients not simultaneously refractory to an immunomodulatory (IMiD) agent and a proteasome inhibitor to 5.6 months for penta-refractory patients who are

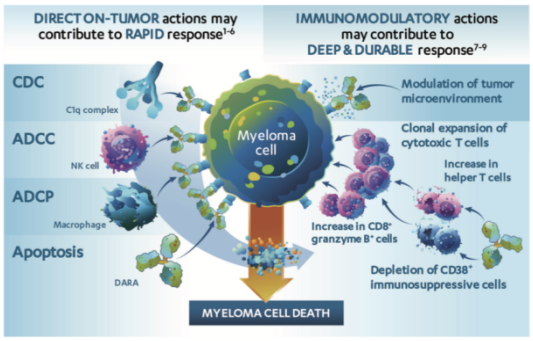
refractory to CD38 MoABs, 2 proteasome inhibitors, and 2 IMiDs.[17] These studies highlight that heavily pre-treated MM patients who are resistant to daratumumab have overall poor prognosis. Thus, research has focused on understanding markers and predictors of daratumumab response and mechanisms of daratumumab resistance, which will prove to be even more important as daratumumab is being moved to frontline therapy.

1.2 Background on the Investigational Product(s) and Associated Known Toxicities

Daratumumab

Non-clinical studies

Daratumumab, the first-in-class CD38 monoclonal antibody, has significantly improved the treatment response of MM, due to plasma cell overexpression of protein CD38. CD38 is highly expressed on myeloma cells but is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic origin, making it a relevant target for the treatment of multiple myeloma. Daratumumab is an immunoglobulin G1kappa (IgG1k) human mAb that binds to a unique CD38 epitope on CD38-expressing cells with high affinity and was developed by the immunization of human immunoglobulin transgenic mice with recombinant CD38 protein.[7,18] Daratumumab binds CD38 with high affinity and induces tumor cell death through a variety of immune-mediated mechanisms including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis, direct apoptosis after cross-linking, and can modulate CD38 enzymatic activity.[7,19] Preclinical studies have showed that daratumumab's ADCC is highly specific to CD38 given daratumumab has not shown to induce ADCC in CD38 negative cells. Preclinical studies have also shown that daratumumab is effective at inducing both CDC and ADCC against MM cells in the presence of bone marrow stromal cells suggestive of daratumumab's activity in the bone marrow microenvironment.[7,18] Daratumumab has also shown to induce apoptosis with cross-linking. In addition, studies have shown that daratumumab has additional antimyeloma effects through immunomodulation and by eliminating a population of highly immunosuppressive CD38$^+$ Tregs, T-cell MDSCs, and Bregs and thus stimulating T-cell effector functions.[19] The immunomodulatory effects of daratumumab not only include reduction of CD38$^+$ immunosuppressive cellular populations, but also include concomitant induction of helper and cytotoxic T-cell expansion, production of IFN-gamma in response to viral peptides, and increased TCR clonality and T-cell functional response suggestive of an improved adaptive immune response.[19]



In-vitro studies, using bone marrow mononuclear cells from patients with multiple myeloma (MM), demonstrated increased killing of tumor cells when daratumumab was combined with lenalidomide or bortezomib as well as with both lenalidomide and bortezomib. Additionally, the upregulation of CD38 by pomalidomide or lenalidomide can enhance the activity of anti-CD38 antibodies including daratumumab. These observations suggest a strong potential for the treatment of CD38-expressing malignancies using daratumumab as monotherapy and in combinations.

The potential toxicity of daratumumab was evaluated in a repeat dose study in chimpanzees. The primary toxicities identified in chimpanzees were infusion-related reactions during the first, but not subsequent, daratumumab infusions and thrombocytopenia. The binding affinity of daratumumab is ≥15-fold higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. Depletion of specific lymphocyte phenotypic cell populations, as expected, based on the intended pharmacological effect of daratumumab, was observed in chimpanzees. No genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted.

Clinical Studies and Efficacy

The promising preclinical data demonstrating the immunomodulatory effects of daratumumab has lead to extensive clinical trials testing the safety and efficacy of daratumumab in initially RRMM and now more recently newly diagnosed MM both transplant eligible and transplant ineligible.

Daratumumab was initially approved in 2015 as monotherapy for patients with MM who have received at least 3 lines of therapy, including a proteasome inhibitor, IMiD, or who are double-refractory to a proteasome inhibitor and IMiD.[9] Pooled analysis of GEN501 and SIRIUS trials evaluating daratumumab monotherapy show an ORR of 31%, median DOR of 7.6 months, median PFS and OS of 4 months and 20.1 months respectively in heavily pretreated RRMM patients.[10,20] The DRd and DVd regimens are approved by the FDA for use in patients with MM who have received at least one prior therapy based on the POLLUX and CASTOR trials respectively.[11,21] POLLUX trial showed a higher ORR in the daratumumab arm, 93% vs 76%, and superior PFS of 83% vs 60%.[11] CASTOR trial showed higher ORR of 84% vs 63% in the daratumumab arm and improved PFS of 16.7 vs 7.1 months.[21] DPd is approved for use in patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor with an ORR of 60% based on the EQUULEUS trial.[22] Daratumumab is also approved in combination with bortezomib, melphalan, and prednisone (VMP) for the treatment of newly diagnosed MM patients who are ineligible for autologous stem cell transplant (ASCT) based on the ALCYONE study which showed a 50% reduction in the risk of progression or death compared with VMP alone.[13] Daratumumab in combination with lenalidomide and dexamethasone was recently approved in newly diagnosed MM patients who are ineligible for ASCT based on the MAIA trial showing a superior ORR in the daratumumab arm of 92.9% vs 81.3% and showing reduced risk of disease progression or death by 44% in the daratumumab arm.[14] The CASSIOPEIA trial in Europe found that daratumumab in combination with VTd compared to VTd alone demonstrated superior sCR of 29% vs 20%, superior CR of 39% vs 26%, and superior achievement of minimal residual disease (MRD) negativity of 64% vs 44%.[15] This lead to the recent FDA approval of D-VTD for the treatment of newly diagnosed patients with MM who are eligible for ASCT. Given this was the first study showing the clinical benefit of daratumumab plus standard of care in frontline treatment of transplant eligible patients with newly diagnosed MM, this has lead to the ongoing GRIFFIN trial studying daratumumab plus standard of care in United States VRd in frontline treatment of transplant eligible patients (NCT02874742).

Daratumumab by intravenous (IV) infusion is currently approved in over 90 countries worldwide for the treatment of relapsed or refractory, and frontline MM. Daratumumab subcutaneous (SC) was developed to provide several potential benefits for both patients and healthcare providers and was approved based on the phase 3 non-inferiority, randomized COLUMBA study. Both co-primary endpoints, overall response rate and C_{trough} at Cycle 3 Day 1, were non-inferior for SC daratumumab, compared to IV daratumumab. Advantages of the subcutaneous form include shorter administration time of 3 to 5 minutes (compared with 4 to 7 hours for IV infusion) and the lower rate of infusion related reactions (IRRs) give additional flexibility and reduction in treatment burden to the patient, as well as reducing health care professional time spent on administration. The smaller administration volume for daratumumab SC reduces the risk of volume overload in patients with cardiac or renal insufficiency.

There is very little data at this time regarding the re-treatment of daratumumab in patients with RRMM who have previously been treated with daratumumab. There was a retrospective analysis recently published regarding the safety and efficacy of daratumumab in combination with pomalidomide and dexamethasone in patients who were daratumumab and/or pomalidomide-refractory. Cohort 1 (12 patients) was daratumumab- and POM-naive, and cohort 2 (22 patients) was daratumumab- and/or POM-refractory. A subgroup of 12 patients in cohort 2 (cohort 3) was daratumumab- and pomalidomide-refractory. The overall response rates (ORRs) were 91.7%, 40.9%, and 33.3% in cohorts 1, 2, and 3, respectively.[23] There is no published data regarding retreatment with daratumumab monotherapy. There is an ongoing trial, Son of SAR study (NCT02514668), evaluating the efficacy of isatuximab monotherapy,

another CD38 monoclonal antibody with similar efficacy to daratumumab monotherapy[24], in patients previously treated with daratumumab. Preliminary unpublished results of this ongoing trial show a response rate of < 10%.

Overall, an estimated 5,528 subjects have received daratumumab in the clinical development program from 37 studies, ie, 8 completed, 19 studies with completed primary analysis (of these, 3 studies have ongoing cohorts), and 10 full ongoing monotherapy and combination therapy clinical studies in newly diagnosed MM, smoldering MM, relapsed/refractory MM, and also non-myeloma diseases, including myelodysplastic syndrome (MDS), amyloidosis, lung cancer, acute lymphoblastic leukemia, natural killer T-cell lymphoma (NKTCL), and non-Hodgkin's lymphoma (NHL), as well as an early-access study and healthy volunteers. Of these, 1,756 subjects were exposed to daratumumab from monotherapy studies and 3,772 subjects were exposed to daratumumab from combination therapy (IB; version 16, dated 20 December 2019).

Pharmacokinetics

Daratumumab is given intravenously (IV) at 16 mg/kg dose and when given as monotherapy for MM, is given once weekly for total of 8 doses (weeks 1-8), every 2 weeks for 8 doses (weeks 9-24), and every 4 weeks thereafter (starting week 25 and onwards). A study that reported the pharmacokinetic data from GEN501 and SIRIUS studies found that in both studies, daratumumab exhibited nonlinear pharmacokinetic characteristics. Decreasing daratumumab clearance with increasing dose suggests saturation of target-mediated clearance at higher dose levels, whereas decreasing clearance over time with repeated dosing may be due to tumor burden reductions as CD38-positive cells are eliminated. These and other pharmacokinetic data analyses support the use of the recommended dose regimen of daratumumab (16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter) to rapidly saturate target-mediated clearance during weekly dosing and maintain saturation when dosing every 2 or 4 weeks.[25]

Analysis of daratumumab pharmacokinetics have showed that daratumumab exhibits typical pharmacokinetics for an IgG1 monoclonal antibody. Mean serum concentrations of daratumumab peaked at the end of the first infusion and then declined in an apparent bi-exponential manner. V_Z estimates indicate that daratumumab is confined primarily in the vascular system, with limited extravascular tissue distribution. Following the first full infusion, C_{max} increased in approximate proportion to the increasing dose of daratumumab 1–24 mg/kg, and increased in a greater than dose-proportional manner after multiple doses. AUC increased in a greater than dose-proportional manner after the first and multiple doses. Following the 16 mg/kg recommended dosing regimen (weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter), accumulation of daratumumab continued throughout the weekly dosing period and decreased slightly as patients entered the less intense dosing periods. Following the end of treatment, daratumumab remained detectable in most patients in the SIRIUS 16 mg/kg group at 8 weeks post-treatment. No subjects in the GEN501 or SIRIUS studies developed antibodies to daratumumab during treatment suggesting a low risk for immunogenicity with this therapeutic agent.[25]
Over the dose range from 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg in combination with other treatments, increases in area under the curve (AUC) were more than dose-proportional. Clearance was rapid at low doses and slower at higher doses; clearance also decreased with multiple doses. This PK profile was consistent with target-mediated disposition indicating target saturation at higher doses.[26] Decreasing clearance over time with repeated dosing may be due to a reduction of tumor burden as $CD38^+$ cells are eliminated.[25] The PK of daratumumab was similar following monotherapy and combination therapies in multiple myeloma. The mean ± SD estimated terminal half-life of daratumumab associated with linear clearance was 18 ± 9 days when administered as monotherapy and 23 ± 12 days when administered as combination therapy.

Exposure-response analyses described elsewhere (Xu et al, submitted)[26] indicates that most patients (approximately 80%) following the recommended 16 mg/kg dose regimen were expected to achieve daratumumab serum concentrations correlated with 99% target (CD38) saturation and 90% of the maximal effect on ORR.[25]

The clinical pharmacology assessment of daratumumab SC monotherapy data are available from daratumumab SC-dosed subjects in a Phase 1/1b study MMY1004 [Part 2]) and Phase 3 study (MMY3012), Phase 2 combination therapy study MMY2040 and population pharmacokinetics and exposure-response analyses. In MMY1004, the 1800 mg dose achieved maximum Ctrough (Cycle 3 Day 1 predose) values that were similar or greater than the maximum Ctrough observed for the approved 16 mg/kg IV dose following the same dose schedule. The PK data from Part 2 supported the daratumumab SC 1800 mg dose selection for the Phase 3 study. The PK data from MMY3012 study demonstrated that daratumumab SC 1800 mg is non-inferior to daratumumab IV 16 mg/kg in terms of maximum Ctrough (Cycle 3 Day 1 predose), with the lower bound of the 90% CI for the geometric means ratio for daratumumab SC versus daratumumab IV for maximum Ctrough (Cycle 3 Day 1 predose) exceeding 80%, thereby meeting the predefined non-inferiority criterion.

Additionally, daratumumab SC 1800 mg monotherapy consistently produced lower peak-to-trough fluctuations, similar or slightly higher trough levels over time, and lower peak concentrations compared with daratumumab IV 16 mg/kg monotherapy. Overall, consistent daratumumab concentrations were observed across the body weight ranges. As expected, slightly higher concentrations were observed for subjects with lower body weights. There was no apparent relationship between exposure and safety endpoints (SAEs, Grade 3 or higher TEAEs and neutropenia).

The simulated trough concentrations following 6 weekly doses of daratumumab SC 1800 mg for combination therapy (daratumumab SC, bortezomib, melphalan, and prednisone [D-VMP], daratumumab SC, lenalidomide, and dexamethasone [D-Rd], daratumumab SC, bortezomib, lenalidomide, and dexamethasone [D-VRd]) were similar to monotherapy.

Overall, daratumumab SC was well-tolerated with manageable side effects and a significantly reduced incidence of IRRs relative to daratumumab IV. The safety profile of daratumumab administered subcutaneously at a flat dose of 1800 mg continued to be generally comparable to that of the 16 mg/kg IV formulation.

Safety

The most frequently reported adverse reactions (reported at a rate of ≥ 20%) in the POLLUX trial were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory traction infections, muscle spasm, cough, and dyspnea.[11] The most frequently reported adverse events (reported at a rate of ≥ 20%) in the CASTOR trial were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, and peripheral sensory neuropathy. Neutropenia and thrombocytopenia are also side effects of daratumumab.[21]

The safety results from all ongoing studies of daratumumab are summarized (through June 2017) below:

Table 1-1 Available Safety Findings in Ongoing Daratumumab Clinical Trials Through 30 June 2017

Study Number (N exposed to Daratumumab)	Safety Results
Daratumumab Monotherapy Trials	
MMY2002, GEN501, and MMY1002 (Relapsed/Refractory MM, 156) Integrated analysis	• **Most common TEAEs**: fatigue (40%), nausea and anemia (28% each), back pain (26%), cough (24%), neutropenia (23%), pyrexia (22%), upper respiratory tract infection (22%), and thrombocytopenia (21%). • **Grade 3/4 TEAEs** in 57% of subjects; most common were anemia (17%), thrombocytopenia (14%), neutropenia (12%), lymphopenia and pneumonia (6%), leukopenia and hypertension (5% each), hypercalcemia (3%). • **TEAEs leading to DC of study treatment** in 4% of subjects; none considered drug related. • **SAEs** in 34% of subjects; most common were pneumonia (6%) and pyrexia, general physical health deterioration, and hypercalcemia (3% each). • **Deaths** due to progressive disease (7%), and 3 (2%) due to TEAEs (cardiorespiratory arrest in the setting of H1N1 influenza, general physical health deterioration secondary to aspiration pneumonia, and pneumonia). None of the fatal TEAEs were considered related to daratumumab.
SMM2001 (smoldering MM, 122)	• SAEs were reported for 15 subjects (24% in the long intense, 2% in intermediate, and 10% in short intense treatment groups). No **IRRs** or **deaths**.
MMY1004 - Relapsed/Refractory MM (subcutaneous administration, 53)	• A total of 8 subjects received daratumumab-MD 1200 mg and 45 subjects received daratumumab- MD 1800 mg. • **Most common TEAEs** (≥20% of all subjects): upper respiratory tract infection (1200 mg: 38%; 1800 mg: 22%), insomnia (1200 mg: 38%; 1800 mg: 11%), decreased appetite (1200 mg: 38%; 1800 mg: 7%), thrombocytopenia (1200 mg: 38%; 1800 mg: 18%), viral upper respiratory tract infection (1200 mg: 25%; 1800 mg: 13%), vomiting (1200 mg: 25%; 1800 mg: 13%), hyperuricaemia (1200 mg: 25%; 1800 mg: 2%), hypokalaemia (1200 mg: 25%; 1800 mg: 4%), blood creatinine increased (1200 mg: 25%; 1800 mg: 4%), anemia (1200 mg: 25%; 1800 mg: 33%), fatigue (1200 mg: 25%; 1800 mg: 20%), pyrexia (1200 mg: 25%; 1800 mg: 27%), diarrhea (1200 mg: 25%; 1800 mg: 22%), headache (1200 mg: 25%; 1800 mg: 18%), cough (1200 mg: 25%; 1800 mg: 13%), epistaxis (1200 mg: 25%; 1800 mg: 4%), hypertension (1200 mg: 25%; 1800 mg: 7%), rhinitis allergic (1200 mg: 25%; 1800 mg: 2%), nasal congestion (1200 mg: 25%; 1800 mg: 2%), rectal hemorrhage (1200 mg: 25%; 1800 mg: 0%), and asthenia (1200 mg: 13%; 1800 mg: 20%), • **Grade 3/4 TEAEs**: in 63% and 49% of subjects in the 1200 mg and 1800 mg cohorts, respectively. The most frequently reported Grade 3 or 4 TEAEs were in the Blood and Lymphatic System Disorders System Organ Class (SOC), reported in 38% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively. Two of 8 (25%) subjects in the 1200 mg cohort and 4% in the 1800 mg cohort had Grade 3 or 4 hypertension. • **SAEs:** SAEs were reported in 26% of all subjects: 50% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively. The most frequently reported serious TEAEs were in the Infections and Infestations SOC (1200 mg: 38%, 1800 mg: 16%), the Nervous System Disorders SOC (1200 mg: 13%, 1800 mg: 4%), and the Respiratory, thoracic and mediastinal disorders (1200 mg: 13%, 1800 mg: 2%). • **No TEAEs leading to DC of study treatment**. One subject in the daratumumab-MD 1800 SC cohort died within 30 days of the last dose of study drug from progressive disease.

MMY3010 (Relapsed/Refractory MM, 687)	• **SAEs** in 38% of subjects; most common were pneumonia (4%), hypercalcemia (3%), pyrexia (3%), dyspnea (2%), thrombocytopenia (2%), acute kidney injury (2%), and back pain (2%). • **Deaths:** Forty-eight subjects (7%) reported TEAEs with an outcome of death.
LYM2001 (non-Hodgkin's lymphoma, 36)	• All subjects had at least 1 or more TEAE. Most common TEAEs were reported from SOC of respiratory, thoracic and mediastinal disorders; cough (DLBCL cohort: 47%; FL cohort: 38%; MCL cohort: 80%); SOC of gastrointestinal disorders: abdominal pain (DLBCL cohort: 13%; FL cohort: 31%; MCL cohort: 20%), and nausea (DLBCL cohort: 33%; FL cohort: 6%; MCL cohort: 40%), and SOC of general disorders and administration site conditions; fatigue (DLBCL cohort: 27%; FL cohort: 19%; MCL cohort: 20%), and pyrexia (DLBCL cohort: 13%; FL cohort: 25%; MCL cohort: 40%) • **SAEs** in 15 subjects. All SAEs were reported in 1 subject each, except for febrile neutropenia, pneumonia, general physical health deterioration, and pyrexia (2 subjects each). • **Deaths** in 4 subjects: 2 due to progressive disease and 2 due to an adverse event (chronic kidney disease and pneumonia). • **IRRs** – none.
Daratumumab Combination Trials	
GEN503 and MMY3003 (integrated; daratumumab in combination with lenalidomide and dexamethasone (318)	• **Most common TEAEs** (DRd treatment group**)**: neutropenia (64%), diarrhea (53%), upper respiratory tract infection (37%), fatigue (37%), anemia (36%), cough (34%), muscle spasms (31%), constipation (31%), thrombocytopenia (29%), viral upper respiratory tract infection (29%), nausea (28%), and pyrexia (25%). • **Grade 3/4 TEAEs** (DRd treatment group**)**: 89%; most common, neutropenia (58%), anemia (16%), and thrombocytopenia (14%). • **TEAEs leading to DC of treatment** in 13% of subjects in the DRd treatment group; most common were pneumonia (4 subjects, 1.3%), general physical health deterioration (3 subjects, 0.9%), and septic shock (2 subjects, 0.6%). • **SAEs** (DRd treatment group**)** in 63% of subjects; most common were pneumonia (13%), influenza, febrile neutropenia (4%) and pyrexia (4% each), and bronchitis, pulmonary embolism, lower respiratory tract infection, diarrhea (3% each). • **Deaths (**DRd treatment group**)**:7% of subjects died within 30 days of the last dose of study drug: 21 due to TEAEs and 1 due to disease progression.
MMY1001 (daratumumab in combination with pomalidomide and dexamethasone, 240)	• **Most common TEAEs**: neutropenia (81%), anemia (55%), fatigue (52%), diarrhea (50%), thrombocytopenia (43%), cough (41%), leukopenia (39%), constipation (36%), nausea (34%), dyspnea (33%), pyrexia (33%), upper respiratory tract infection (32%), muscle spasms (29%), vomiting (28%), arthralgia (26%). • **Grade 3 or 4 TEAEs** in 99% of subjects; most common were neutropenia (79%), anemia (28%), leukopenia (24%), thrombocytopenia (19%), lymphopenia (14%), and pneumonia and fatigue (13% each). • **TEAEs leading to DC of treatment** in 16% of subjects (no single AE reported in >1 subject). • **SAEs** in 57% of subjects; most common were pneumonia (12%), sepsis (7%), febrile neutropenia (5%), fall (4%), anemia, dyspnea, small intestinal obstruction, and urinary tract infection (3% each). • **Deaths:** 9% of subjects died during study treatment or within 30 days after the last dose of study drug; 7 due to AEs and 2 deaths due to disease progression.

MMY1001 (daratumumab plus bortezomib and dexamethasone, 30)	• **SAEs** were reported for 3 subjects in the DVd arm (Hyperglycemia [1 subject], soft tissue infection, pneumonia, prerenal failure, diarrhea, respiratory failure [1 subject], laboratory test interference [1 subject]. In DVMP arm, SAEs were reported in 1 subject (cardiac failure). No subjects in the D-VTd arm were reported to have SAEs. • No **deaths** reported.
MMY1001 (daratumumab in combination with carfilzomib/dexamethasone +/- lenalidomide DKd = 20, DKRd = 20)	• **AEs of Interest** – Cardiac Events: In the DKd arm, cardiac disorder TEAEs of interest were reported in 15% of subjects; 4 (5%) subjects had a Grade 3 or Grade 4 event. No cardiac disorder TEAEs of Grade 5 was reported. In the DKRd arm, cardiac disorder TEAEs of interest were reported in 41% of subjects, with 1 subject (5%) having a Grade 3 or Grade 4 event (congestive heart failure) that was also an SAE. No Grade 5 events were reported. • **SAEs** reported in 32% of subjects in the DKd arm (n=85); most common was pneumonia (7%). SAEs were reported in 46% of subjects in the DKRd arm (n=22). The most frequently reported SAEs were pulmonary embolism (n=3; 14%) and influenza and pyrexia (n=2; 9% each). All other SAEs were reported in 1 subject each. • One **death** in the DKd arm due to progressive disease.
MMY1005 (daratumumab in combination with bortezomib and dexamethasone; Japan, 8)	• **SAEs** in 3 subject each (herpes zoster, prostate cancer, nasopharyngitis). • No **IRRs.** • No **deaths.**
MMY3004 (daratumumab in combination with bortezomib and dexamethasone, 243)	• **Most common TEAEs** were thrombocytopenia (60%), peripheral sensory neuropathy (50%), diarrhea (35%), upper respiratory tract infection (33%), anemia (28%), and cough (28%). • **Grade 3/4 AEs** were reported in 81% of subjects; most common were thrombocytopenia (46%), anemia (15%), and neutropenia (14%). • **TEAEs leading to DC of treatment** were reported for 10% of subjects; most common were pneumonia (4 subjects; 2%), and cardiac failure congestive (2 subjects; 0.8%). • **SAEs** in 50% of subjects; most common were pneumonia (10%), and anemia, bronchitis, thrombocytopenia, atrial fibrillation, upper respiratory tract infection, and pyrexia (3% each). • **Deaths**:15 subjects died within 30 days of the last dose of study drug; 13 deaths were due to TEAEs and 2 were due to disease progression.
MMY3007 (daratumumab in combination with bortezomib, melphalan and prednisone, 700)	• **Most common TEAEs** were thrombocytopenia (51%), neutropenia (51%), anemia (33%), peripheral sensory neuropathy (31%), diarrhea (24%), pyrexia (22%), nausea (21%), upper respiratory tract infection (20%) and constipation (18%). • **Grade 3/4 TEAEs** were reported in 74% of subjects, with neutropenia (39%) and thrombocytopenia (36%) being the most frequently reported. • **SAEs** were reported in 37% of subjects, with pneumonia being the most frequent (7%). • **Deaths**: Thirty-eight (5%) subjects had a Grade 5 TEAE.
MMY3008 (daratumumab in combination with lenalidomide and dexamethasone, 729)	• **Most common TEAEs** were neutropenia (39%), diarrhea (34%), constipation (33%), fatigue (28%), anemia (25%), nausea and edema peripheral (24% each), insomnia (22%), muscle spasms (21%), and asthenia (20%). • **Grade 3/4 TEAEs** were reported in 70% of subjects, with neutropenia being the most frequently reported (32%). • **SAEs** were reported in 50% of subjects; most common were pneumonia (6%), pyrexia and pulmonary embolism (3% each). • **Deaths** Thirty-four subjects (5%) had a Grade 5 TEAE.

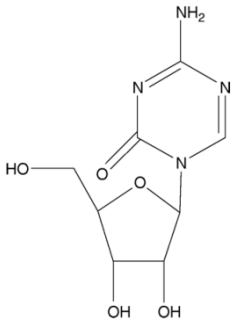
Monitoring response on Daratumumab

Daratumumab has been found to interfere with serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) assays due to co-migration of daratumumab with patients' M protein which impedes accurate quantification of endogenous M proteins.[18,27] Given this can pose a problem when SPEP and IFE assays are needed to measure disease response, a clinical assay known as the daratumumab IFE reflex assay (DIRA) has been developed to mitigate daratumumab interference with IFE.[27] DIRA uses a mouse anti-daratumumab antibody that binds to daratumumab and shifts the migration of daratumumab away from the M protein.[27] The DIRA assay has been utilized in clinical trials of daratumumab to confirm disease response, and the assay's specificity, reproducibility, and ability to distinguish daratumumab mAb from endogenous M protein has been validated.[9]
In summary, daratumumab has been well tolerated and has demonstrated encouraging response rates in clinical trials both as a single agent and in combination regimens in the relapsed/refractory setting and now more recently in the frontline setting. Moreover, daratumumab in combination regimens has maintained a favorable safety profile without significant increase in toxicities.

Azacitidine

Azacitidine is FDA approved for the treatment of all subtypes of myelodysplastic syndrome (MDS) and was recently approved in 2018 in combination with venetoclax for newly diagnosed AML in patients who were ≥ 75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy.

Azacitidine is thought to have two main mechanisms of antineoplastic action—cytotoxicity, resulting from incorporation into RNA and DNA, and DNA hypomethylation, restoring normal growth control and differentiation in hematopoietic cells. Induction of DNA hypomethylation appears to require lower azacitidine doses than does cytotoxicity, as the concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not suppress DNA synthesis. Upon uptake by cells, azacitidine is phosphorylated to 5-azacytidine monophosphate by uridine-cytidine kinase and then to diphosphate and triphosphate by pyrimidine monophosphate and diphosphate kinases, respectively. 5-azacitidine triphosphate is incorporated into RNA, disrupting nuclear and cytoplasmic RNA metabolism and inhibiting protein synthesis. 5-azacitidine diphosphate is reduced by ribonucleotide reductase to 5-azacitidine-deoxycytidine diphosphate, which is then phosphorylated by nucleoside diphosphate kinases to 5-azadeoxycitidine triphosphate, which is incorporated into DNA. As a result, DNA synthesis is inhibited. Azacitidine is most toxic during the S-phase of the cell cycle, but the predominant mechanism of cytotoxicity has not been established. Azacitidine inhibits methylation of replicating DNA by stoichiometric binding with DNA methyltransferase 1, resulting in DNA hypomethylation. DNA hypermethylation at the CpG islands has been described in myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), and other malignancies.



Molecular structure of Aza

Clinical Studies

Effectiveness of azacitidine in high risk MDS was demonstrated in azacitidine-001, a Phase III international, multicenter, randomized controlled trial comparing azacitidine administered subcutaneously (SubQ) at 75 mg/m2 for 7 consecutive days every 28 days to conventional care regimen (CCR) which included either best supportive care, low dose cytarabine, or intensive chemotherapy as selected by investigators before randomization for 358 patients with high risk MDS.[28] After a median follow-up of 21.1 months, the median overall survival was 24.5 months for the

azacitidine group vs 15 months for the conventional care group. Azacitidine resulted in higher rates of hematologic responses assessed by International Working Group (IWG) 2000 criteria and longer durations of response with median of 13.6 months in the azacitidine group compared to 5.2 months in the conventional care group. At 2 years, 50.8% of patients in the azacitidine group were alive compared with 26.2% in the conventional group.[28] Azacitidine prolonged OS compared with CCR regardless of IPSS cytogenetic risk group. Subset analysis of the data has shown that the drug can be used safely in even the oldest patients with MDS and is superior to treatment with other established regimens, such as low-dose cytarabine.[29] Azacitidine-001 showed that achievement of hematologic response was associated with improved OS with azacitidine treatment, and patients who achieved a hematologic response to azacitidine had significantly prolonged OS and reduced risk of death versus patients who achieved a response to CCR. In addition, stable disease or achievement of complete response (CR), marrow CR (mCR), partial response (PR) or hematologic response with alternative dosing schedules of azacitidine has been shown to significantly reduce the risk of death versus disease progression. In the azacitidine-001 study, the median time to first response with azacitidine was 2 cycles (range: 1–16), with 91% of responding patients achieving first response within 6 cycles and all but 1 achieving first response by cycle 12. Continued treatment improved response quality in 48% of patients, with a median of 3 cycles from first to best response. By cycle 12, 92% of responding patients achieved their best response.[28] Based on this experience, some clinicians have advised administering at least six cycles of azacitidine, and the National Comprehensive Cancer Network guidelines for MDS recommend at least four to six cycles of azacitidine before assessing for treatment failure.

Studies performed by Cancer and Leukemia Group B (CALGB) demonstrated that azacitidine had activity in MDS and AML when given at 75 mg/m^2 by intravenous infusion (CALGB 8421) or subcutaneous injection (CALGB 8921 and 9221) daily for 7 days in a 28-day cycle.[30,31] The crossover phase III CALGB 9221 trial which was a multicenter randomized, open-label trial designed to compare the safety and efficacy of subcutaneous azacitidine with supportive care (observation group) in patients with any of the five subtypes of MDS, showed a significant effect of azacitidine on response rates ($P< 0.0001$), with an overall response rate of 60% in patients receiving azacitidine compared with 5% in those receiving only supportive care. Median time to leukemic transformation or death was 21 months for azacitidine arm versus 13 months for supportive care arm. Transformation to acute myelogenous leukemia occurred in 15% of patients on the azacitidine arm and in 38% of patients in the supportive care arm. Median OS was 18 months for azacitidine and 11 months for supportive care arm.[30,31] Response rates in these CALGB trials were similar in subjects with all MDS subtypes and with AML.

In a sub-analysis of azacitidine-001 of low-blast- count AML (20%–30% blasts) the 2-year OS rate for patients treated with azacitidine was 50%, and the median OS was 24.5 months compared with 16.0 months for patients treated with CCR and 16.4 months for patients not preselected to receive intensive chemotherapy (best supportive care or low-dose cytarabine). Survival benefits with azacitidine may not require CR because CR rates were similar for azacitidine versus CCR (18% vs. 16%), whereas rates of red blood cell transfusion independence were significantly higher with azacitidine (41% vs. 18%).[32]

Recently, the global phase III randomized open-label azacitidine- AML-001 study of azacitidine (75 mg/m^2 per day on days 1–7 in 28-day cycles) versus CCR extended these findings in patients aged ≥65 years with newly diagnosed AML with >30% blasts. Azacitidine treatment demonstrated a clinically meaningful improvement in median OS of 10.4 months versus 6.5 months with CCR. Azacitidine significantly improved 1-year survival: 46.5% versus 34.2% with CCR, a 12.3% difference. In patients who did not achieve CR, median OS was prolonged from 6.9 months with azacitidine versus 4.2 months with CCR.[33]

Azacitidine in combination with venetoclax was approved in newly diagnosed AML in elderly patients ≥ 75 years of age or patients who had comoribidities that precluded the use of intensive induction chemotherapy based on M14-358 (NCT02203773), a large multicenter phase 1b dose-escalation and expansion study showing that the novel

combination of venetoclax with decitabine or azacitidine was effective and well tolerated in elderly patients with AML. With a median time on study of 8.9 months, 67% of patients (all doses) achieved complete remission (CR) + CR with incomplete count recovery (CRi), with a CR + CRi rate of 73% in the venetoclax 400 mg + HMA cohort. Patients with poor-risk cytogenetics and those at least 75 years old had CR + CRi rates of 60% and 65%, respectively. The median duration of CR + CRi (all patients) was 11.3 months, and median overall survival (mOS) was 17.5 months; mOS has not been reached for the 400-mg venetoclax cohort.[34]

Azacitidine in Multiple Myeloma

While azacitidine is currently not approved in MM, there have been pre-clinical studies studying the role of azacitidine and DNMTi in MM. Studies have found that the DNA methylation score can predict for the sensitivity of human myeloma cell lines and primary MM cells of patients to DNMTi.[35] Azacitidine has also been shown to exert apoptosis-inducing and growth-inhibiting effects on MM cell lines and its mechanism may be related to the decrease of BCL-2/BAX ratio, caspase-3 activation, and the arrest of the cell cycle.[36] Another study found that azacitidine induces apoptosis of MM cells by downregulating two crucial cell survival pathways in MM by inhibiting the elaboration of IL-6 receptor alpha and IL-6 resulting in reduced expression of phosphor-STAT3 and Bcl-xl and by inhibiting both nuclear factor-kappaB nuclear translocation and DNA binding.[37]
Clinically DNMTi's such as azacitidine are currently being investigated in MM as monotherapy and in combination with standard therapies such as lenalidomide and dexamethasone (NCT01155583, NCT01050790). A recent phase 1b single center 3 x 3 dose escalation study looking at oral azacitidine (CC-486) in combination with lenalidomide and dexamethasone in patients with RRMM who had previously failed lenalidomide found the ORR was 37.5% at the MTD and clinical benefit rate was 50%. Median OS was 10.3 months and median PFS was 2.6 months. This study found that oral azacitidine, lenalidomide, and dexamethasone produced meaningful clinical responses in heavily treated Len refractory MM patients.[38] However to this data there has been no trial assessing the safety and efficacy of daratumumab in combination with azacitidine and dexamethasone.

Standard Dosing

The standard dose of azacitidine, based on the trials leading to its approval in AML and MDS, is 75 mg/m^2 intravenously or subcutaneously for 7 days every 28 days.[28,30,31,34] Because of the difficulty of continued administration for 7 days, in a randomized trial, MDS patients were given azacitidine subcutaneously in one of three schedules every 4 weeks for six cycles: azacitidine 5-2-2 (75 mg/m^2 daily for 5 days, followed by 2 days of no treatment, and then 75 mg/m^2 daily for 2 days for a total dose of 525 mg/m^2 per cycle), azacitidine 5-2-5 (50 mg/m^2 daily for 5 days, followed by 2 days of no treatment, and then 50 mg/m^2 daily for 5 days for a total dose of 500 mg/m^2 per cycle), or azacitidine 5 (75 mg/m^2 for 5 days for a total dose of 375 mg/m^2).[39] All three alternative dosing regimens produced hematological improvements, red blood cell transfusion independence, and safety responses consistent with the approved azacitidine regimen. However, results suggest that the azacitidine 5 dosing regimen may be better tolerated with a more convenient dosing schedule than the two alternative dosing regimens.[39]

Safety

With respect to safety of azacitidine, in the CALGB 9921 trial, >95% patients in both groups reported treatment-associated adverse events. azacitidine-treated subjects reported more frequently than observation arm subjects gastrointestinal events (nausea, vomiting, diarrhea, constipation, and anorexia), neutropenia, febrile neutropenia, thrombocytopenia, injection site events, arthralgia, dizziness, dyspnea, cough, and myalgia. Serious adverse events occurred more frequently in azacitidine-treated patients (60%) than in observation patients (36%). Serious adverse events most commonly resulting in hospitalization were thrombocytopenia, febrile neutropenia, fever, and pneumonia. There were no deaths attributed to azacitidine treatment. During the study periods, half of the deaths in the three trials were probably related to MDS and the other half were unrelated to MDS.[31]

The most common reasons for azacitidine discontinuation, dose reduction, or therapy interruption were leukopenia, neutropenia, and thrombocytopenia. Patients who developed CR or PR first had further decreases in hematologic parameters. Most patients in both treatment arms received packed RBC and/or platelet transfusions and medications to treat adverse events. The frequency of adverse events decreased after the first two cycles of azacitidine therapy.[31]

The data described below reflect exposure to azacitidine for injection in 443 MDS patients from 4 clinical studies. Study 1 was a supportive-care controlled trial (subcutaneous administration), Studies 2 and 3 were single arm studies (one with subcutaneous administration and one with intravenous administration), and Study 4 was an international randomized trial (subcutaneous administration).

Table below presents adverse reactions occurring in at least 5% of patients treated with azacitidine for Injection in Study 4. Similar to Studies 1 and 2 described above, duration of exposure to treatment with azacitidine for Injection was longer (mean 12.2 months) compared with best supportive care (mean 7.5 months).

Table 1-2 Adverse Reactions Occurring In At Least 5% of Patients Treated With Azacitidine for Injection

	Number (%) of Patients			
	Any Grade		Grade 3/4	
Body System Adverse Reactions[a]	**Azacitidine for Injection (N=175)**	**Best Supportive Care Only (N=102)**	**Azacitidine for Injection (N=175)**	**Best Supportive Care Only (N=102)**
Blood and lymphatic system disorders				
Anemia	90 (51)	45 (44)	24 (14)	9 (9)
Febrile neutropenia	24 (14)	10 (10)	22 (13)	7 (7)
Leukopenia	32 (18)	2 (2)	26 (15)	1 (1)
Neutropenia	115 (66)	29 (28)	107 (61)	22 (22)
Thrombocytopenia	122 (70)	35 (34)	102 (58)	29 (28)
Gastrointestinal disorders				
Abdominal pain	22 (13)	7 (7)	7 (4)	0
Constipation	88 (50)	8 (8)	2 (1)	0
Dyspepsia	10 (6)	2 (2)	0	0
Nausea	84 (48)	12 (12)	3 (2)	0
Vomiting	47 (27)	7 (7)	0	0
General disorders and administration site conditions				
Fatigue	42 (24)	12 (12)	6 (3)	2 (2)
Injection site bruising	9 (5)	0	0	0
Injection site erythema	75 (43)	0	0	0
Injection site hematoma	11 (6)	0	0	0
Injection site induration	9 (5)	0	0	0
Injection site pain	33 (19)	0	0	0
Injection site rash	10 (6)	0	0	0
Injection site reaction	51 (29)	0	1 (1)	0
Pyrexia	53 (30)	18 (18)	8 (5)	1 (1)
Infections and infestations				
Rhinitis	10 (6)	1 (1)	0	0
Upper respiratory tract infection	16 (9)	4 (4)	3 (2)	0
Urinary tract infection	15 (9)	3 (3)	3 (2)	0
Investigations				
Weight decreased	14 (8)	0	1 (1)	0

Metabolism and nutrition disorders				
Hypokalemia	11 (6)	3 (3)	3 (2)	3 (3)
Nervous system disorders				
Lethargy	13 (7)	2 (2)	0	1 (1)
Psychiatric disorders				
Anxiety	9 (5)	1 (1)	0	0
Insomnia	15 (9)	3 (3)	0	0
Renal and urinary disorders				
Hematuria	11 (6)	2 (2)	4 (2)	1 (1)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	26 (15)	5 (5)	6 (3)	2 (2)
Dyspnea exertional	9 (5)	1 (1)	0	0
Pharyngolaryngeal pain	11 (6)	3 (3)	0	0
Skin and subcutaneous tissue disorders				
Erythema	13 (7)	3 (3)	0	0
Petechiae	20 (11)	4 (4)	2 (1)	0
Pruritus	21 (12)	2 (2)	0	0
Rash	18 (10)	1 (1)	0	0
Vascular disorders				
Hypertension	15 (9)	4 (4)	2 (1)	2 (2)

In Studies 1, 2 and 4 with subcutaneous administration of azacitidine for injection, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of azacitidine for injection. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of subcutaneous treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

Overall, adverse reactions were qualitatively similar between the intravenous and subcutaneous studies. Adverse reactions that appeared to be specifically associated with the intravenous route of administration included infusion site reactions (e.g. erythema or pain) and catheter site reactions (e.g. infection, erythema, or hemorrhage).

Most Commonly Occurring Adverse Reactions (Subcutaneous or Intravenous Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by intravenous route also included petechiae, rigors, weakness and hypokalemia.

Pharmacokinetics

In terms of pharmacology of azacitidine, it is rapidly absorbed following subcutaneous administration. Maximum plasma concentration is attained in about 30 minutes. Azacitidine is widely distributed, and is rapidly eliminated, with a mean plasma half-life of about 41 minutes.[40]

Metabolism of azacitidine involves deamination by cytidine deaminase followed by opening of the ring structure.[41] Azacitidine and its metabolites are primarily excreted by the kidneys. The effects of intrinsic factors such as age, gender, race, renal impairment, or hepatic impairment on the pharmacokinetics of azacitidine have not been studied. *In*

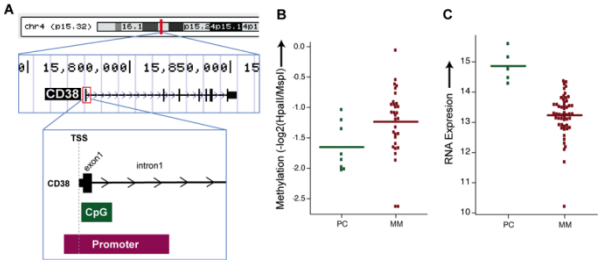
vivo drug-drug interaction studies have not been conducted.[40] *In vitro* studies in cultured human hepatocytes indicate that azacitidine at a clinically relevant concentrations is not an inducer of CYP 1A2, 2C19, or 3A4/5.[40]

1.3 Rationale for the Proposed Study

While daratumumab is well tolerated and has high efficacy, not all patients respond and many patients eventually develop progressive disease and resistance to daratumumab. These patients often have poor prognosis and limited treatment options. A retrospective study presented at ASH 2018 looking at MM patients who have progressed on daratumumab found that these patients have a median OS of 5.3 months and a post-daratumumab regimen ORR of 34% with limited treatment options. Another study analyzing outcomes of 275 MM patients at 14 academic centers with disease refractory to CD38 MoABs (daratumumab and isatuximab) found a median OS for the entire cohort of 8.6 months ranging from 11.2 months for patients not simultaneously refractory to an IMiD agent and a proteasome inhibitor to 5.6 months for penta-refractory patients (refractory to CD38 MoAb, 2 PIs, and 2 IMiDs). Overall response rate to first regimen after relapse post CD38 MoAB was 31% with median PFS and OS of 3.5 and 9.3 months. These studies demonstrate that MM patients refractory to CD38 MoAb such as daratumumab have poor prognosis and limited treatment options. Thus developing ways to improve the efficacy of daratumumab and overcome the resistance to daratumumab are very much in need, especially as trials have progressively lead to daratumumab's approval not only in the relapsed refractory setting but also in the frontline setting for MM patients.
Pre-clinical data shows that CD38 expression on MM cells is associated with response to daratumumab therapy and a significant association has been seen between CD38 expression and daratumumab-mediated antibody-dependent cellular cytotoxicity (ADCC) as well as complement-dependent cytotoxicity (CDC) in ex vivo patients' samples with MM.[42,43] Pre-clinical data also shows that there is rapid but reversible loss of cell surface CD38 expression on MM cells during daratumumab treatment which may subsequently lead to immune escape and resistance to daratumumab and thus disease progression.[19,43] There are several possible explanations for the reduction of CD38 levels during daratumumab treatment: 1) daratumumab may select for tumor cells with lower CD38 expression while preferentially eliminating MM cells with high CD38 levels 2) downregulation of CD38 may be an active process to evade daratumumab-mediated killing 3) in vitro studies suggest that binding of daratumumab to CD38 may cause redistribution of CD38 molecules 4) trogocytosis of CD38-daratumumab complexes and direct internalization may also result in a loss of CD38. This pre-clinical data showing that CD38 is a predictor of response to daratumumab and that loss of CD38 occurs during daratumumab treatment, suggests that methods to upregulate CD38 expression can increase the efficacy of daratumumab and decrease the resistance and immune escape to daratumumab. Thus efforts are underway to study the regulation of CD38 in MM.

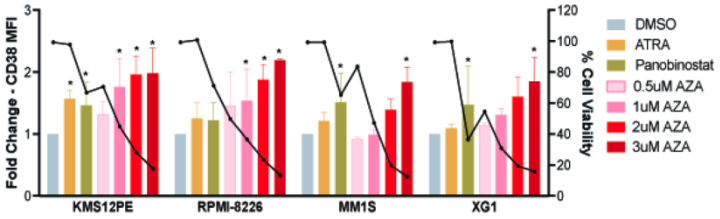
Recent studies have shown that DNA methylation patterns change during MM progression, and clinically aggressive subtypes such as plasma cell leukemias and high risk (4,14) MM have hypermethylation.[44-46] DNA hypermethylation has been associated with heterochromatin formation and inactivation of tumor suppressor genes.[47] DNA methyltransferases (DNMTs) methylate cytosine residues in CpG islands and remodel chromatin. Currently two DNMT inhibitors (DNMTis) have been approved for treatment of acute myeloid leukemia and myelodysplastic syndrome: azacitidine and decitabine (DEC). These cytidine analogs function by incorporating into genome of proliferating cells during DNA synthesis, covalently binding DNMTs, targeting them for proteasomal degradation and causing passive loss of cytosine methylation in daughter cells.[47]

Based on analysis of publicly-available ENCODE data, Dr. Arun Wiita's lab at UCSF found a CpG island in the first exon of CD38 and hypothesized that DNA methylation represses CD38 expression. CD38 was previously identified as a differentially methylated region in myeloma patient samples with a negative



CpG island, DNA methylation and expression of CD38 gene

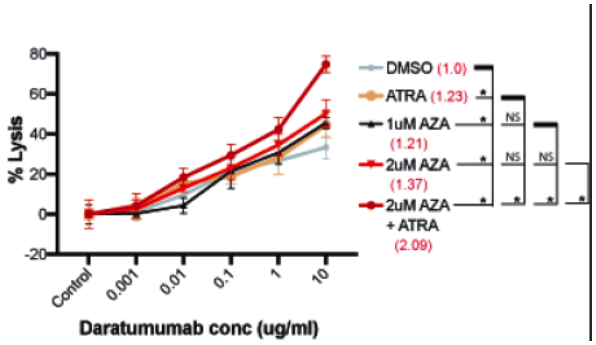
correlation between gene expression and DNA methylation.[45] Dr. Wiita's lab performed additional analysis of DNA methylation and gene expression data in three independent MM datasets and found an inverse correlation between CD38 promoter methylation status and gene expression between normal plasma cells and malignant plasma cells in MM. These findings supported our hypothesis of methylation-level regulation of CD38 transcription, and suggested that DNMTi treatment with azacitidine may be able to increase CD38 transcription in MM cells and that this increase can be exploited to augment the efficacy of daratumumab-mediated lysis of MM cells.



Aza treatment increases CD38 cell surface expression

To test the role of DNA methylation in regulation of CD38 expression, a panel of MM cell lines were treated with increasing doses of DNMTi azacitidine, and CD38 cell surface expression was measured by flow cytometry. Cells were treated for either 3 days or 5 days with flow cytometry analysis at 7 days, which allowed for DNMTi incorporation into newly synthesized DNA in replicating cells leading to DNMT degradation and loss of DNA methylation. This has induced a 1.2-2.4 increase in CD38 MFI in a dose dependent manner across all four cell lines. Importantly, at doses of > 1μM azacitidine appears to upregulate CD38 equally if not more than previously investigated doses of the known inducers ATRA and Panobinostat.[42,48]

Next we determined whether upregulated CD38 MFIs increased functional daratumumab efficacy. Using an immortalized transgenic NK cell line to mediate lysis, we observed a significant increase in antibody dependent cellular cytotoxicity (ADCC) against DNMTi treated vs control. Importantly, this increase in ADCC was consistent with CD38 MFI upregulation. For example, 2 μM azacitidine increased CD38 MFI 1.37 ± 0.03 fold and increased ADCC lysis to 50.23 ± 6.84 %. In addition, the additive effect of DNMTi and ATRA on CD38 upregulation was also seen in ADCC assays.



Treatment with Aza significantly increases ADCC of Dara and the effect is additive with ATRA

Pre-clinical data from Dr. Wiita's lab shows that by de-repressing the transcription of CD38 and upregulating the expression of CD38 on MM plasma cells, azacitidine can potentially increase the ADCC and efficacy of daratumumab in MM patients and help reverse daratumumab resistance that develops over time caused by loss of CD38 expression. However, there is no prior trial that has assessed the safety and efficacy of daratumumab combined with azacitidine for treatment of MM. This is the first study designed to assess the safety and efficacy of azacitidine combined with daratumumab and dexamethasone to see if the synergy of azacitidine and daratumumab, through upregulation of CD38 expression, can improve the efficacy of daratumumab alone and overcome the resistance to daratumumab that develops over time.

The main risk of this trial and combining azacitidine and daratumumab is toxicity, particularly cytopenias and infections, though we anticipate that the combination will be safe and there are clear dose modifications and safety stopping rules in place for DLTs. The safety lead-in to the trial will allow for formal safety analysis in the beginning of the trial and mitigate the risks of toxicity and ensure that the patients enrolled in this phase II study are treated with a dose combination of azacitidine and daratumumab with an acceptable safety profile. Daratumumab has already been approved in MM and demonstrated adequate safety in combination with other agents such as revlimid, pomalidomide, and velcade. Azacitidine is approved in MDS and leukemia and demonstrated an acceptable safety profile in other non-myeloma hematologic malignancies in combination with other agents that also cause cytopenias such as venetoclax.[34] It is anticipated that the combination of daratumumab and azacitidine, which have acceptable safety

profiles for currently approved indications, will have a manageable safety profile in combination. We believe that the potential benefits of improving response rates, CR rates, PFS and OS of relapsed refractory MM patients with poor prognosis by combining daratumumab and azacitidine outweighs the risks of possible increased toxicity with this combination.

1.4 Rationale for the Dose Selection/Regimen

Daratumumab will be administered subcutaneously at the currently approved dose of 1800 mg, once weekly for 8 doses, then every two weeks for 8 doses, and then every 4 weeks thereafter until disease progression or unacceptable toxicity. First dose will be administered on Day 1 of Cycle 1. The rationale behind this dosing regimen stems from the GEN501 and SIRIUS trials that evaluated the safety and efficacy of daratumumab monotherapy.[10,20] An analysis to understand and justify the recommended dose and dosing schedule for daratumumab in MM patients from a quantitative pharmacologic perspective was done. This analysis found that there was a maximum effect relationship between daratumumab exposure (i.e. maximal trough concentration) and overall response rate (ORR) and between daratumumab and target saturation.

The daratumumab subcutaneous dose of 1800 mg was chosen based on the COLUMBA study[49] which showed that subcutaneous daratumumab was non-inferior to intravenous daratumumab in terms of efficacy and pharmacokinetics and had a consistent safety profile to that of intravenous daratumumab in patients with relapsed refractory multiple myeloma An overall response was seen in 108 (41%) of 263 patients in the subcutaneous group and 96 (37%) of 259 in the intravenous group (relative risk 1·11, 95% CI 0·89–1·37). The geometric means ratio for C_{trough} was 107·93% (90% CI 95·74–121·67), and the maximum C_{trough} was 593 µg/mL (SD 306) in the subcutaneous group and 522 µg/mL (226) in the intravenous group.

Azacitidine will be given subcutaneously or IV at standard dose 75 mg/m^2 for 5 days consecutively every 4 weeks starting day -7 to day -3 of Cycle 1 (before first dose of daratumumab). The starting dose regimen of 75 mg/m^2 is based on prior trials leading to azacitidine approval in MDS and AML, including the azacitidine-001[28] and CALGB 8421, 8921, and 9221 trials.[30,31] The dosing of azacitidine for 5 days consecutively (instead of 7) will be used for both patient convenience and to minimize toxicity. This is based on a study that showed that 5 days of consecutive azacitidine had similar efficacy to 7 days.[39] Azacitidine prescribing information created by Celgene suggests dose adjustments for azacitidine based on hematologic toxicity and our dose de-escalation follows these recommendations.[50] Dexamethasone 40 mg will be given orally once weekly on days 1, 8, 15, and 22 of each four-week cycle starting day 1 of cycle 1 for at least the first two cycles. Dose modifications for azacitidine and dexamethasone based on toxicities are outlined in Section 5.5 There will be no dose modification for daratumumab. Treatment will be continued until progression or patient unable to tolerate treatment due to toxicities.

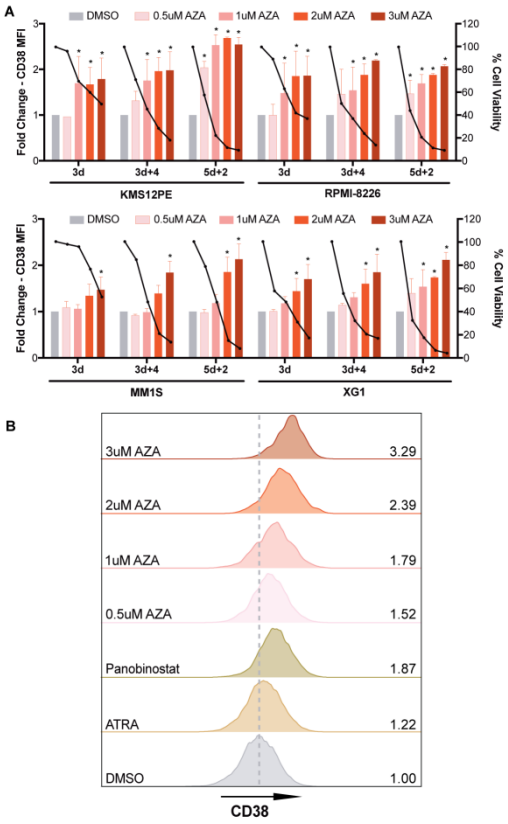


Figure: Azacitidine upregulates *CD38* transcript expression. (A) Bar graph showing fold change in CD38 RNA (red) and cell surface protein (blue) in RPMI-8226 cells upon drug treatments. Data from 3d+4 and 5d+2 azacytidine treatments are grouped together and compared to ATRA and panobinostat treatment. Data is presented as mean ± SD from a representative experiment from two independent experiments. (B) CD38 expression on primary MM cells upon azacytidine treatment. Grey lines separate different patient samples (IDs on *x*-axis). Colors in the legend indicate the drug and concentration used. The percentage of CD138+ cells in each sample are given in brackets underneath the IDs. Data are presented as mean ± SD from 3 replicate wells.

1.5 Correlative Studies

The correlative studies for this trial stem from preclinical work done in Dr. Arun Wiita's lab at UCSF. Dr. Priya Choudhry and Dr. Arun Wiita's work was recently published in *Leukemia* and is described below.

1) To determine the *in vivo* change in CD38 expression on plasma cells in MM patients exposed to azacitidine (primary objective)

Hypothesis: Exposure to azacitidine will result in an increased surface expression of CD38, as determined by flow cytometry.

Pre-clinical work done in Dr. Arun Wiita's lab where a panel of MM cell lines (RPMI-8226, MM.1S, XG-1, KMS12-PE) were treated with increasing doses of azacitidine and CD38 cell surface expression was analyzed by flow cytometry, showed that azacitidine consistently increased an increase in D38 median fluorescent intensity (MFI) in all cell lines. Wiita's lab treated cells for either 3 days or 5 days with flow cytometry analysis at 7 days (3d+4 or 5d+ 2, respectively). This extra time allowed for DNMTi incorporation into newly synthesized DNA in replicating cells over two doublings, leading to DNMT degradation and loss of DNA methylation. 3d+4 and 5d+2 treatments induced a 1.2-2.4 fold increase in CD38 MFI in a dose dependent manner for all four cell lines. 3 uM azacitidine, which is clinically equivalent to 75 mg/m^2, consistently induced at least a 2 fold increase in CD38 MFI in all cell lines, in both the 3d+4 and 5d+2 treatments.

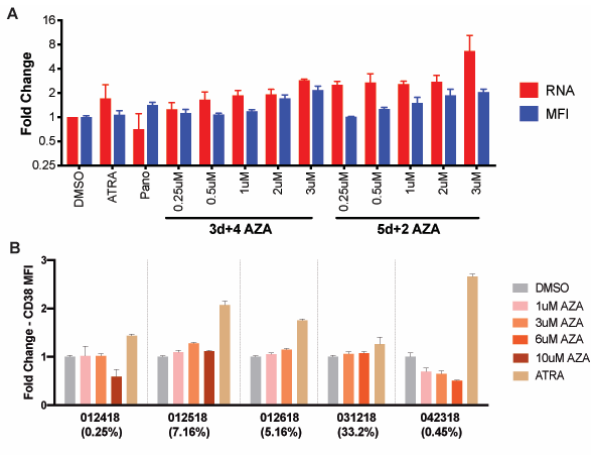


Figure: Azacitidine treatment increases CD38 cell surface expression. (A) Bar graph of CD38 expression and cell survival upon treatment with azacytidine in the indicated cell lines. For each cell line the 3d, 3d+4 and 5d+2 treatments are compared side-by-side. Height of the bars indicates the fold change in CD38 MFI (left y-axis) and bold black line shows % cell viability (right *y*-axis). Both are normalized to DMSO treatment. Colors indicate the concentration of azacytidine used. Data are presented as mean ± SD from 2-3 independent experiments with triplicates in each experiment. * indicates a significant difference from DMSO treatment ($p \leq 0.05$ using a paired student's *t*-test). (B) shows the histogram plots for CD38 expression for one representative experiment in XG1 cells. Histograms from 3d+4 azacytidine treatment are compared to the known CD38 upregulators ATRA and Panobinostat. The drugs used are indicated on the left, and fold change in CD38 MFI compared to DMSO control is given on the right. The grey dotted line indicates MFI in DMSO treated cells.

The preclinical work done in Dr. Wiita's lab further demonstrates that azacitidine also increases CD38 transcription in treated RPMI-8226 cells using qRT-PCR thus leading to its increased expression. Intriguingly, treatment with azacitidine appeared to induce higher fold changes in CD38 expression at the RNA level compared to cell surface expression. This indicates that there may be additional mechanisms regulating CD38 expression post-transcriptionally. Though azacitidine is cleared very rapidly with respect to its pharmacokinetics, we hypothesize that the transcriptional effects of azacitidine will be prolonged and long-lasting due to incorporation into DNMT's and subsequent effects of drug on methylation after cellular division.
The following correlative studies will be done contingent upon funding.

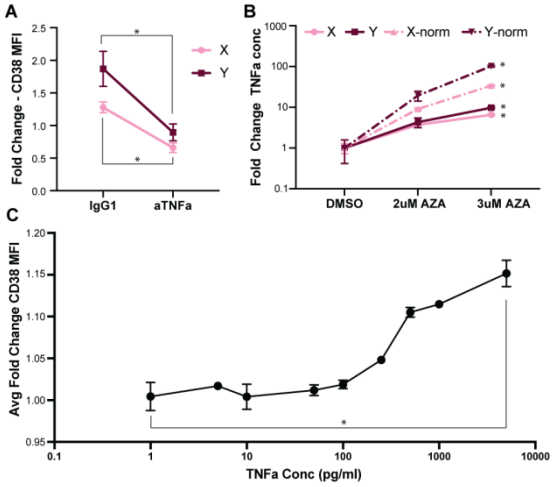
2) To assess *in vivo* changes in whole genome methylation, including CD38 specific methylation, after treatment with azacitidine via performing whole genome reverse-phase bisulfite sequencing.

Hypothesis: Exposure to azacitidine will result in decreased overall methylation of the plasma cell genome and thus indirectly lead to increased CD38 expression.

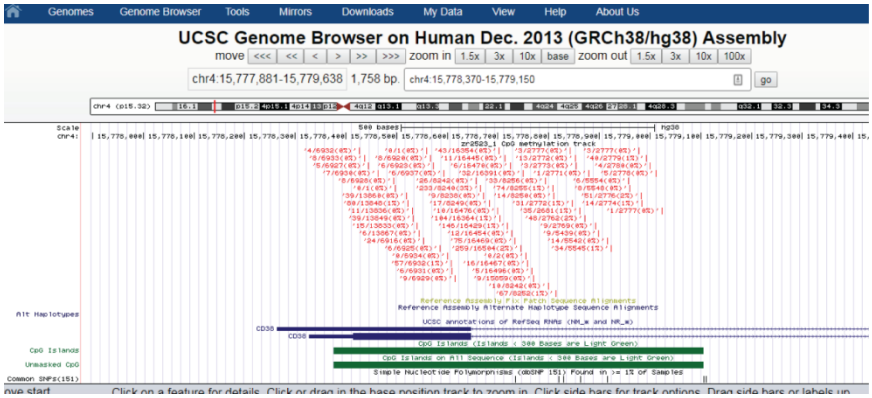
Historically, determination of DNA methylation was largely confined to only a small fraction of the DNA methylome, usually to regulatory regions like gene promoters which are frequently associated with the CpG-rich CpG islands.[51] Initially, based on analysis of publicly-available ENCODE data, Dr. Wiita's lab found a CpG island in the first exon of CD38 and hypothesized that DNA methylation represses CD38 expression. CD38 was previously identified as a differentially methylated region in myeloma patient samples with a negative correlation between gene expression and DNA methylation. They further performed additional analyses of DNA methylation and gene expression data in three independent MM datasets (GSE43860, GSE17306 and GSE12453) and found an inverse correlation between CD38 promoter methylation status and gene expression between normal plasma cells and malignant plasma cells in MM. These findings suggested that DNMTs may regulate CD38 transcription.

However, surprisingly in Dr. Wiita's pre-clinical work, targeted bisulfite sequencing of the CD38 CpG island revealed almost complete hypomethylation at baseline in RPMI-8226 and KMS12-PE cells. Thus it was hypothesized that DNMTi treatment might instead upregulate CD38 indirectly. It was tested whether azacitidine upregulates CD38 via transcription factors PU.1 or ATF2 or through activation of interferon response, but this was not found to be true. It was tested whether DNMTi might function via TNF∝ upregulation given TNF∝ is regulated by DNA methylation and is known to upregulate CD38 expression in airway smooth muscle cells. Co-treatment with a TNF∝-neutralizing antibody completely abrogated azacitidine-induction of CD38 upregulation. Furthermore, azacitidine treatment indeed induced TNF∝ secretion from RPMI-8226 cells. Finally, recombinant TNF∝ increased surface CD38 in RPMI-8226

cells. These results therefore confirm that indirect mechanisms can mediate DNMTi-induced CD38 upregulation and suggest the TNF∝ pathway may play a leading role in this process. We anticipate that there may be other indirect mechanisms by which DNMTi treatment upregulates CD38 and by doing whole genome reverse-phase bisulfite sequencing in patients pre and post azacitidine treatment, we hope to assess for other genes that may be involved in CD38 upregulation that are regulated by methylation. Many approaches to analyze the DNA methylome include a bisulfite conversion step during which unmethylated cytosines are converted to uracil, while methylated cytosines remain as cytosines. Subsequent PCR manifests unmethylated cytosines as thymines, thus, allowing discrimination between the unmethylated and methylated cytosines. The gold standard to address the complete DNA methylome is whole genome bisulfite sequencing (WGBS).[51]



AZA induces CD38 upregulation via TNFα upregulation. (A) RPMI-8266 were co-treated with 3 μM AZA treatment and either IgG1 (control) or a neutralizing anti-TNFα antibody (αTNFα). Data are represented as Fold Change in CD38 cell surface expression upon 3 μM AZA treatment normalized to DMSO treatment for the same Antibody treatment. αTNFα completely blocks surface induction of CD38 after Aza treatment. * indicates a significant difference between CD38 Fold change in IgG1- versus αTNFα- treated cells in individual experiments ($p \leq 0.05$ using a paired student's *t*-test). (B) TNFα concentrations were measured in supernatants from RPMI-8266 cell line after Aza treatment. Data are represented as fold change in TNFα concentration compared to DMSO. X and Y represent independent experiments, and data are presented as mean ± SD from triplicate wells. X-norm and Y-norm are data from independent replicate experiments X and Y normalized to the live cell concentration measured at the time of supernatant collection. * indicates a significant difference between values from 3 μM AZA treatment and DMSO control ($p \leq 0.05$ using a paired student's *t*-test). (C) Fold change in CD38 cell surface expression after 72-hour treatment of RPMI-8226 cells with exogenously added recombinant TNFα. Data are represented as mean ± SEM of two independent experiments. * indicates a significant difference ($p \leq 0.05$ using a paired student's *t*-test).



***CD38* CpG methylation at baseline.** Targeted Bisulfite seq data visualized in UCSC browser. *CD38* RefSeq RNAs and CpG island are depicted in blue and green respectively. The CpG Methylation track highlights each CpG site as a vertical bar. The label on the left of each CpG bar indicates the methylation ratio followed by percent methylation in brackets. For example, the first CpG labeled '4/6932 (0%)' indicates 4 reads were methylated in 6932-fold sequencing read depth of coverage at this site, amounting to 0% methylation ratio. Data for RPMI-8226 is depicted here as an example. KMS12PE cell line was similarly completely hypomethylated.

3) To assess the *in vivo* changes in multiple myeloma tumor microenvironment with treatment of azacitidine via CyTOF

Hypothesis: Azacitidine will lead to changes in the multiple myeloma bone marrow tumor microenvironment that may have immunoregulatory and anti-tumor effects

Azacitidine may upregulate expression of CD38 indirectly through altering the bone marrow tumor microenvironment, specifically through upregulation of inflammatory cytokines such as TNF alpha. Given the limited clinical data with regards to the use of azacitidine in multiple myeloma patients, there is very little known about the in vivo impact of azacitidine on bone marrow stromal tumor microenvironment. In leukemia, pre-clinical data shows that azacitidine has a variety of immunomodulatory effects on leukemic cell lines including upregulation of CD86, downregulation of INDO, downregulation of PI-9, downregulation of MHC-class I molecules, upregulation of PD-1, and increase of CXCR4.[52]Another study looking at azacitidine's epigenetic effects found that azacitidine inhibits T-cell proliferation and activation, blocking cell cycle in the G_0 to G_1 phase and decreasing the production of proinflammatory cytokines such as tumor necrosis factor alpha and interferon gamma. The immunomodulatory effects of azacitidine have lead to an exploration of its role in the allogeneic transplantation setting in prevention of graft versus host disease. Pre-clinical studies have shown that azacitidine has a direct effect on immune response through affecting T-cell activation, proliferation, and secretion of proinflammatory cytokines. The effect of 5-azaC in T lymphocytes, which is caused by both an early effect on the expression of genes related to T-cell proliferation and activation and a delayed effect on the methylation pattern of genes such as *FOXP3*, lead to the hypothesis 5-azaC may play a role in the allogeneic transplantation setting as an immunomodulatory drug.[53] A clinical study of 27 patients who had undergone a reduced intensity allogeneic transplantation for acute myeloid leukemia and were treated with monthly courses of azacitidine, found that administration of azacitidine increased the number of Tregs within the first 3 months after transplantation compared with a control population. azacitidine administration also induced a cytotoxic CD8(+) T-cell response to several tumor antigens and thus this study further examined the role of azacitidine after transplantation as a mechanism of augmenting a graft versus leukemia effect without a concomitant increase in graft versus host disease.[54]

Given that much of Dara's effects are mediated based on interactions with NK cells and macrophages (to clear the CD38-coated plasma cells) or modulating the microenvironment (potentially depleting specific NK subsets and Tregs), examining shifts in immune microenvironment after Azacitidine could play an important role in dissecting clinical effects of azacitidine and may help explain either increased or decreased efficacy of dara combination beyond that expected from CD38 upregulation alone. These findings could also inform possible combinations of azacitidine with other immunotherapies in the future.

We propose to use CyTOF (Fluidigm) or mass cytometry to better understand the effects of azacitidine on the bone marrow tumor microenvironment. CyTOF, is a variation of flow cytometry in which antibodies are labeled with heavy metal ion tags rather than fluorochromes. Readout is by time-of-flight mass spectrometry. This allows for the combination of many more antibody specificities in a single samples, without significant spillover between channels.

2 Study Objectives

2.1 Hypothesis

We hypothesize that in patients with relapsed and refractory multiple myeloma who have previously progressed on daratumumab, the combination of azacitidine, daratumumab, and dexamethasone will be effective and safe and lead to improved response rates through upregulation of CD38.

2.2 Primary, Secondary, and Exploratory Objective(s)

Primary Objectives:

The primary objective of this study is to evaluate the efficacy of adding azacitidine to daratumumab and dexamethasone, as measured by the overall response rate in patients with relapsed refractory multiple myeloma (RRMM) previously treated with daratumumab.

Secondary Objectives:

- To evaluate the duration of response per IMWG criteria.
- To evaluate the safety and tolerability of azacitidine in combination with daratumumab and dexamethasone.
- To evaluate progression free and overall survival in patients treated with azacitidine in combination with daratumumab and dexamethasone.
- To assess the changes in CD38 expression on plasma cells after treatment with azacitidine and correlate this change with the depth and duration of response of azacitidine in combination with daratumumab and dexamethasone.

2.3 Primary, Secondary, and Exploratory Endpoint(s)

Primary endpoints:

- Rate of overall response (ORR) defined as sCR+CR+VGPR + PR as best response utilizing IMWG Uniform Response Criteria[55] calculated in the time period from initiation of study treatment until discontinuation of treatment

Secondary Endpoints:

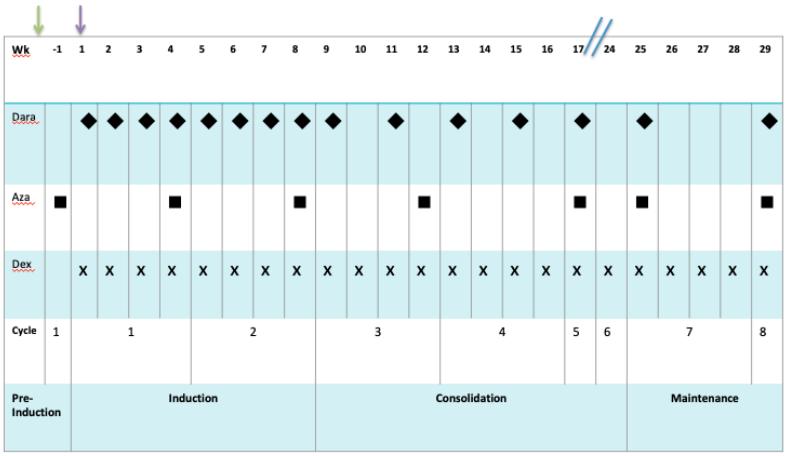
- Adverse events, as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0), assessed from the initiation of study treatment until discontinuation of treatment
- Duration of response (DOR) defined as the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the IMWG criteria or death due to PD whichever occurred first.
- Overall survival which is defined from the date of first dose of study treatment to the date of death due to any cause or censored based on the date of last encounter if patient is alive or lost to follow-up.
- Progression-free survival which is defined as the duration from the date of first dose of study treatment to the date of first documented evidence of progressive disease or death, whichever occurs first.
- Change in CD38 surface expression of plasma cells after azacitidine treatment (the CD38 expression of plasma cells pre and post first cycle of azacitidine treatment in this trial will be compared)
- Number of patients who achieve at least 1.5 fold increase in their CD38 expression by flow cytometry after azacitidine treatment
- Correlation of change in CD38 expression after azacitidine treatment to response including depth of response and duration of response

3 Study Design

3.1 Characteristics

This is a single-arm, open label, 2-stage phase II study of the safety and efficacy of daratumumab in combination with azacitidine and dexamethasone in RRMM patients who have previously been treated with daratumumab with a safety lead-in cohort. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

Patients will need a washout period of at least 6 months from their most recent exposure to daratumumab prior to first dose of daratumumab on the trial. This 6 month washout period will allow for CD38 normalization[56], and hence will enable the measurement of the change in CD38 expression on plasma cells secondary to azacitidine (secondary endpoint correlative study for this trial) and eliminate the confounding factor of daratumumab's effect on CD38 expression. Patients will receive azacitidine at the standard 75 mg/m^2 dose 5 days consecutively every 4 weeks starting day -7 to day -3 of Cycle 1 and then Day 22-26 of Cycle 1-3, and subsequently Day 1-5 of Cycle 5 and thereafter, with dose modifications for toxicities as outlined in Section 5.5. Daratumumab will be administered at the standard dose of 1800 mg subcutaneously, with first dose administered on day 1. Daratumumab will be dosed in standard fashion: weekly for 8 doses (induction phase), every two weeks for 8 doses (consolidation phase), and then every 4 weeks thereafter (maintenance phase). There will be no dose modifications for daratumumab. Dexamethasone at a dose of 40 mg PO (or IV if PO is not available) will be given weekly for Cycle 1 and 2. This dose may be reduced or stopped after Cycle 2 on non-daratumumab administration weeks and as a pre-medication on daratumumab administration weeks. Further dose reduction is permitted based on dose modification criteria outlined in Section 5.5. Bone marrow biopsies will be done within 14 days of Cycle 1 day -7 (first azacitidine dose) and on Cycle 1 day 1 prior to first daratumumab administration (or after completion of first 5 days of azacitidine and prior to first daratumumab administration), for correlative studies. Please see Section 5 for more details on dosing of study treatment and Section 6 for more details regarding correlative studies.



Dara, Aza, and Dex dosing schedule
Green arrow= Bone marrow biopsy # 1 on Day -7 or within 1 week before first Aza dose
Purple arrow= Bone marrow biopsy #2 on Day 1 before Dara first dose

A Simon's minimax 2-stage design will be used for this study. The study will have an interim halting for safety analysis after enrollment of 6 patients and an interim halting for efficacy analysis after completion of Simon's Stage I with enrollment of 13 patients. Please refer to Section 8 for further details regarding interim analysis, stopping rules, and statistics supporting this design. Safety monitoring will be done throughout the trial per Study Procedures and Schedule of Events.

Response to treatment will be evaluated according to the International Myeloma Working Group (IMWG) response criteria,[55]via standard indices including SPEP, UPEP, immunoglobulin levels, immunofixation, and free light chain assay, at the end of each treatment cycle during induction and consolidation phase and at the end of every two treatment cycles during maintenance phase. See Section 7 for more details on response measurements. Patients will remain on study until they are unable to tolerate treatment due to toxicities or demonstrate progression. At the time of progression, repeat bone marrow biopsy can be obtained at the discretion of the treating hematologist but will not be required by the study.

The anticipated duration of subject participation in this trial is estimated to be 8 months. Patient accrual is estimated to be 12-18 months. Patients will be followed for one year after the last patient has received the last administration of daratumumab. The anticipated duration of the entire study is 3 years.

3.2 Eligibility Criteria

Inclusion Criteria

1. Age ≥18 years

2. Patients must have a known diagnosis of multiple myeloma with evidence of measurable disease, AND have evidence of disease progression based on IMWG criteria[55]:

    - Serum M-protein ≥0.5 g/dL, or urine M-protein ≥200 mg/24 hours. OR
    - In the absence of measurable M-protein, Serum immunoglobulin free light chain ≥10 mg/dL, and abnormal serum immunoglobulin kappa lambda free light chain ratio.

3. Relapsed from or refractory to 2 or more different prior therapies, including immunomodulatory drugs (IMiDs; eg, thalidomide, lenalidomide) and proteasome inhibitors, chemotherapy-based regimens, monoclonal antibodies, or autologous stem cell transplantation (ASCT).
    - Relapse is defined as progression of disease after an initial response (MR or better) to previous treatment, more than 60 days after cessation of treatment
    - Refractory disease is defined as <25% reduction in M-protein or progression of disease during treatment or within 60 days after cessation of treatment

4. Prior exposure to daratumumab, with most recent dose being at least 6 months prior to trial enrollment
5. ECOG performance status <2 (Karnofsky >60% (see Appendix 1)
6. Demonstrates adequate organ function as defined below within 7 days of first dose of drug:

<u>Adequate bone marrow function:</u>	
absolute neutrophil count	≥1,500/mcL
platelets	≥75,000/mcL
<u>Adequate hepatic function:</u>	
total bilirubin	within normal institutional limits, unless elevated due to Gilbert's syndrome and direct bilirubin is within normal limits
AST(SGOT)	≤3 X institutional upper limit of normal
ALT(SGPT)	≤3 X institutional upper limit of normal
<u>Adequate renal function:</u>	
creatinine	≤ 1.5 x within institutional upper limit of normal

OR

creatinine clearance	GFR ≥ 60 mL/min/1.73 m^2, calculated using the Cockcroft-Gault equation, unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m^2

7. Life expectancy of at least 3 months.
8. Women of childbearing potential must have at least one negative highly sensitive serum (β eta-human chorionic gonadotropin [β eta-hCG]) during screening, within one week prior to the first dose of any component of study treatment

9. Before enrollment, a woman must be either:
    a. Not of childbearing potential defined as:
    - Postmenopausal:
        - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level (>40 IU/L or mIU/mL in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
    - Permanently Sterile
        - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

OR

b. Of childbearing potential and
- Practicing 2 highly effective user-independent methods of contraception (failure rate of <1% per year when used consistently and correctly
- Examples of highly effective user-independent methods of contraception include:
    - implantable progesterone-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)
- Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

- Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

- Agrees to remain on a highly effective method for 4 weeks before the first dose of any component of study treatment, throughout the study (including during dose interruptions), and for 4 weeks following discontinuation of azacitidine, and for 3 months after last daratumumab dose

Note: If the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman

must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

- Agrees to not breast feed for the duration of the study (including during dose interruptions), and for 4 weeks following discontinuation of azacitidine, and for 3 months after last daratumumab dose

10. Women must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study (including during dose interruptions), and for 4 weeks following discontinuation of azacitidine, and if receiving daratumumab, for 3 months after the last dose.

11. Due to the teratogenicity of azacitidine and the lack of adequate reproductive toxicity data for daratumumab, in addition to the user independent highly effective method of contraception, a male or female condom with or without spermicide, diaphragm, or cervical cap is required. Male condom and female condom should not be used together (due to risk of failure with friction).

12. During the study (including during dose interruptions), and for 4 weeks following discontinuation of azacitidine, and for 3 months after the last daratumumab dose, in addition to the user independent highly effective method of contraception (even if he has undergone a successful vasectomy), a man
    - Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (ie, latex or synthetic condom with spermicidal foam/gel/film/cream/suppository)
    - Who is sexually active with a woman who is pregnant must use a latex or synthetic condom.
    - Must agree not to donate sperm
13. Willing and able to adhere to the prohibitions and restrictions specified in this protocol and referenced in the ICF.

14. Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

Exclusion Criteria

1. Diagnosed or treated for malignancy (either solid tumor or hematologic) other than multiple myeloma, except:
    - Malignancy treated with curative intent and with no known active disease at enrollment.
    - Adequately treated non-melanoma skin cancer, lentigo maligna or in situ malignancies (including but not limited to, cervical, breast) with no evidence of disease.

2. Received daratumumab therapy less than 6 months prior to trial enrollment
3. Primary refractory to prior daratumumab
4. Subject is:
    a. seropositive for human immunodeficiency virus (HIV)
    b. 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.

c. 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).

5. Known chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal to minimize daratumumab-related pulmonary toxicities.
   Note: FEV1 testing is required for subjects suspected of having chronic obstructive pulmonary disease and asthma. Subjects must be excluded if FEV1 <50% of predicted normal.

6. Known moderate or severe persistent asthma within the past 2 year or currently has uncontrolled asthma of any classification.
   Note: Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study. FEV1 testing is required for subjects suspected of having asthma.

7. Concurrent medical condition or disease (eg, active systemic infection) 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.

8. Clinically significant cardiac disease, including:
   a. Myocardial infarction within 6 months before Cycle 1, Day -7, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class IIIIV).
   b. Uncontrolled cardiac arrhythmia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 5.0 Grade 2 or higher) or clinically significant electrocardiogram (ECG) abnormalities.
   c. Screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec.

9. Known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, daratumumab or its excipients (refer to Investigator's Brochure), or known sensitivity to mammalian-derived products.

10. Concurrent plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and/or skin changes), or light chain amyloidosis.

11. Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.

12. Contraindications to the use of daratumumab, azacitidine or dexamethasone per local prescribing information

13. Taken any disallowed therapies as noted in Section 6, Pre-study and Concomitant Therapy before the planned first dose of study drug

14. Received any therapy to treat cancer (including radiation, chemotherapy, biologics, cellular therapies, and/or steroids at doses > 20 mg) or undergone a major surgical procedure within 14 days, or within 5 half-lives of

an anticancer drug, prior to the first dose of study treatment, whichever is longer (with the exception of palliative radiotherapy for symptomatic management but not on measurable extramedullary plasmacytoma).

15. Participated in an interventional clinical trial(s) and received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before Cycle 1, Day -7 or 5 pharmacokinetic half-lives, whichever is longer

16. Had major surgery within 2 weeks before Cycle 1, Day -7, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration.
    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty is not considered a major surgery

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before Cycle 1 Day -7 (first dose of azacitidine) such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

3.3 Inclusion and Recruitment of Women and Minorities

Individuals of any sex/gender, race, or ethnicity may participate.

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area.

3.4 Duration of Treatment

In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until:

- Disease progression which requires discontinuation of the study treatment;
- Inter-current illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Participant decides to withdraw from the study;
- Significant participant non-compliance with protocol;
- If the participant meets an exclusion criterion (either newly developed or not previously; or, recognized) that precludes further study participation
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Each subject will be followed until 1 year after his/her last dose of study treatment, until death or withdrawal of consent for study participation, whichever occurs first. The end of study is defined as when all subjects have completed either at least 1 year of follow-up, or until death or withdrawal of consent for study participation, whichever occurs first. Further details regarding the long-term follow-up phase are detailed in Section 6.3.3.

3.6 Primary Completion

The estimated primary completion is 18 months after the study opens to accrual.

3.7 Study Completion

The expected study completion date is 30 months after the study opens to accrual.

4 Investigational Products

4.1 Description, Supply and Storage of Investigational Products

Daratumumab

Classification

Anti-CD38 Antibody

Mechanism of Action

Daratumumab is an IgG1κ human monoclonal antibody directed against CD38. CD38 is a cell surface glycoprotein which is highly expressed on myeloma cells, yet is expressed at low levels on normal lymphoid and myeloid cells (Lokhorst 2015). By binding to CD38, daratumumab inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and antibody dependent cellular phagocytosis.

Metabolism

None known

Contraindications

History of severe hypersensitivity (eg, anaphylactic reactions) to daratumumab or any component of the formulation.

Formulation, Appearance, Packaging, and Labeling

Daratumumab and hyaluronidase-fihj, daratumumab-SC will be provided as a fixed-dose (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial. The daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 120 mg/mL as a liquid vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Packaging

Daratumumab is supplied as glass vials containing daratumumab at a concentration of 120 mg/mL for subcutaneous administration.

Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

Availability

Daratumumab is being obtained as study supply provided by Janssen.

Storage and handling

Daratumumab is stored at the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C. Daratumumab must not be utilized after the expiry date printed on the label. The daratumumab product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Refer to the study site investigational product and procedures manual for additional guidance on-study drug preparation, handling, and storage.

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure (IB) and/or product package insert.

Azacitidine

Classification

Hypomethylating agent

Mechanism of Action

Antineoplastic effects may be a result of azacitidine's ability to promote hypomethylation of DNA, restoring normal gene differentiation and proliferation. Azacitidine also exerts direct toxicity to abnormal hematopoietic cells in the bone marrow.

Metabolism

None known

Contraindications

Hypersensitivity to azacitidine, mannitol, or any component of the formulation; advanced malignant hepatic tumors

Formulation, Appearance, Packaging, and Labeling

Azacitidine for injection is supplied as a lyophilized powder in 100 mg single-dose vials packaged in cartons of 1 vial (NDC 0591-2897-49).

Availability

Azacitidine is being obtained as commercial supply

Storage and handling

Azacitidine is stored at unreconstituted vials at 25ºC (77º) with excursions permitted to 15º to 30ºC (59º to 86ºF). Discard unused portion.

Please refer to the package insert [redacted].

Side Effects

Complete and updated adverse event information is available in the current IB and/or product package insert.

Dexamethasone

Classification

Dexamethasone is a potent steroid and direct toxin for malignant plasma cells.

Mechanism of Action

Dexamethasone is a long acting corticosteroid with minimal sodium-retaining potential. It decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

Metabolism

Substrate of CYP3A4 (major), P-glycoprotein/ABCB1; Note: Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; Induces CYP3A4 (weak)

Contraindications

Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections. Documentation of allergenic cross-reactivity for corticosteroids is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

Formulation, Appearance, Packaging, and Labeling

Dexamethasone is supplied as 40 mg tablets for oral administration.

Availability

Dexamethasone is being obtained as commercial supply.

Storage and handling

Dexamethasone is stored at room/ambient temperature. Please refer to manufacturer’s product information for handling and storage conditions of dexamethasone.

Side Effects

Complete and updated adverse event information is available in the current IB and/or product package insert.

4.2 Accountability Records for Investigational Product(s)

UCSF Investigational Drug Services (IDS) will manage drug accountability records for UCSF.

4.3 Ordering Investigational Product(s)

UCSF will obtain daratumumab directly from pharmaceutical company and azacitidine as commercial supply.

5 Treatment Plan

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

Daratumumab

Preparation

Daratumumab-SC will be provided as a fixed-dose (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to the pharmacy and site.

Treatment Schedule and Administration

Daratumumab SC should be given according to product information: [redacted]

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 – 5 minutes in the abdominal subcutaneous tissues in the left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Reasons for continued observation after daratumumab injection may include but are not limited to the following: subjects with a higher risk of respiratory complications (e.g., subjects with mild asthma or subjects with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history), subjects with IRR with the first injection of study drug, subject with decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study.

All administration will be planned as outpatient visits. Subjects will receive pre-injection medications and post-injection medications as detailed in the protocol.

Daratumumab will be administered weekly during induction treatment in Cycles 1 to 2 (Days 1, 8, 15, 22), every 2 weeks during consolidation treatment in Cycles 3 to Cycle 6 (Day 1, 15), and every 4 weeks during maintenance treatment in Cycle 7 (Day 1) and beyond. This schedule is provided below in Table 5-1.

Table 5-1. Daratumumab Administration Schedule

Weeks	Cycle (every 4 weeks)	Schedule
Weeks 1 to 8 (induction)	Cycle 1-2	weekly (total of 8 doses)
Weeks 9 to 24[a] (consolidation)	Cycle 3-6	every two weeks (total of 8 doses)
Weeks 25 onwards until disease progression[b] (maintenance)	Cycle 7 and onwards	every four weeks

[a] First dose of the every-2-week dosing schedule is given at week 9

[b] First dose of the every-4-week dosing schedule is given at week 25

As noted in the Study Procedures and Schedule of Events, vital signs should be monitored extensively on Cycle 1, Day 1 before, during, and after the first administration of daratumumab. For all other administrations, vital signs should be measured before the start of the injection and at the end of the injection. These vital signs will be measured by standard daratumumab subcutaneous protocol. 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.

If an IRR develops, then the injection should be temporarily interrupted or slowed down. In the event of a life-

threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, dara-SC should be discontinued, and no additional dara-SC should be administered to the participant. See section below for instructions on the management of IRR and local ISRs.

Guidelines for Prevention and Management of Administration-Related Reactions and Local Injection-site Reactions of Daratumumab-SC

Pre-dose Medication

All participants will receive the following medications 1 to 3 hours prior to each study drug administration:

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine: diphenhydramine 25-50 mg IV or PO or equivalent. Avoid IV use of promethazine.
    - After Cycle 6, if a participant has not developed an administration-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.
- Corticosteroids (Long-acting or intermediate-acting):
    - *Dexamethasone dosing as part of combination therapy:*
        - Administer 40 mg dexamethasone (or equivalent) prior to every daratumumab injection in the first two cycles. Since dexamethasone is also the background regimen specific corticosteroid for this treatment regimen, the dexamethasone treatment dose will instead serve as pre-medication on daratumumab administration days.
        - Dexamethasone is given orally or intravenously prior to the first daratumumab injection and oral administration may be considered prior to subsequent injections.
    - If the subject does not experience a major systemic administration-related reaction after the first 8 doses of daratumumab, consider discontinuing the administration of corticosteroids as a pre-medication (excluding any background regimen-specific corticosteroid or treatment-specific dexamethasone as determined by the primary treating provider).
    - Further dose reduction of dexamethasone is permitted based on dose modification criteria outlined in Section 5.5.

Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional in Cycle 1 Day 1 and can be administered up to 24 hours before administration as per investigator discretion.
If necessary, all PO pre-administration medications may be administered out of the clinic on the day of the administration, provided they are taken within 3 hours before the administration.

Post-dose Medication

Administer post-dose medication to reduce the risk of delayed administration and injection related reactions as follows:

- Consider administering low-dose methylprednisolone (≤ 20 mg) or equivalent, the day after the administration.
- For participants with a higher risk of respiratory complications (e.g. participants with mild asthma or participants with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history) the following post-administration medication should be considered:
    - Antihistamine (diphenhydramine or equivalent)
    - Leukotriene inhibitor (montelukast or equivalent)
    - Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
    - Control medications for lung disease (e.g. inhaled corticosteroids ± long-acting β2 adrenergic

receptor agonists with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for participants with COPD)

- Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after participants are released from the hospital/clinic. If an at-risk participant experiences no major administration-related reactions, then these post-administration medications may be waived after 4 doses at the investigator's discretion.
- Any post-injection medication will be administered after the injection has completed.

Management of Administration-related Reactions and Local Injection-site Reactions of Daratumumab-SC

Injection-related Reactions (IRRs)

Injection-related reactions (IRRs) are systemic reactions related to daratumumab administration. Participants should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple participants will be dosed at the same time. If an IRR develops during Dara SC administration, then the administration should be temporarily interrupted. Participants who experience AEs during Dara-SC administration must be treated for their symptoms. Participants should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, Dara-SC should be discontinued.

Injection-related Reactions Grade 1 or Grade 2:

If the investigator assesses a Grade 1-2 IRR to be related to administration of study intervention, then the Dara-SC administration should be interrupted. When the participant's condition is stable, Dara-SC administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of Dara-SC administration.
If the participant 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 participant must be permanently discontinued from Dara-SC treatment.

Injection-related Reactions Grade 3 or Higher:

For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the Dara-SC administration must be stopped, and the participant must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the Dara-SC administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of Dara-SC administration.
If the intensity of the AE returns to Grade 3 after restart of the Dara-SC administration, then the participant must be permanently discontinued from Dara-SC treatment.
For IRR AEs that are Grade 4, the Dara-SC administration must be stopped, and the participant permanently discontinued from Dara-SC treatment.

Recurrent Injection-related Reactions:

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent Dara-SC administration, the participant must be permanently discontinued from Dara-SC treatment.

Injection Site Reactions:

In clinical studies, SC administration of daratumumab was associated with local injection site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

Recommended Concomitant Therapy:

- Prophylaxis for Herpes Zoster Reactivation:
  - Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase, as per institutional guidelines. Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting study treatment and continue for 3 months following study treatment. Acceptable antiviral therapy includes acyclovir (eg 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.
- 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 participants at risk for HBV reactivation.
  - In patients who develop reactivation of HBV while on study treatment, suspend treatment with study treatment and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of study treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Azacitidine

Azacitidine should be given at 75mg/m^2 IV/SC for 5 consecutive days starting in cycle 1 day -7 to -3. Subsequently azacitidine will be given for 5 consecutive days on days 22-26 of cycles 1-3. Patients should be premedicated for nausea and vomiting. Cycles should be repeated every 4 weeks with dose modifications as needed per parameters outlined below in Section 5.5.2.1. Starting cycle 5, azacitidine will be given for 5 consecutive days on days 1-5 to coordinate with daratumumab dosing. This protocol uses azacitidine 5 day dosing as opposed to the standard 7 day dosing used in MDS and AML, given that studies have shown equivalent efficacy with 5 day dosing and we hope to minimize cumulative toxicities.[39] Treatment may be continued as long as the patient continues to benefit.

Dexamethasone

Dexamethasone at a dose of 40 mg PO (or IV if PO is not available) will be given weekly for Cycle 1 and 2. This dose may be reduced or stopped after Cycle 2 on both non-daratumumab administration weeks and as a pre-medication on daratumumab administration weeks as per treating physician discretion. Further dose reduction is permitted based on dose modification criteria outlined in Section 5.5.

Subjects may receive low-dose methylprednisolone (≤20 mg) orally (or equivalent in accordance with local standards) for the prevention of delayed IRRs as clinically indicated.

Dose modifications, dose delays, and dose interruptions for study drugs are described in Section 5.5.

5.2 Treatment Compliance

Study drug (daratumumab) will be administered as a subQ injection and study drug (azacitidine) will be administered either as IV or subQ by qualified staff and the details of each administration will be recorded in APEX, the electronic medical record system used at UCSF. Additional details are provided in the study site investigational product and procedures manual. Subjects will be provided with a diary to record intake of dexamethasone; sites will use information to complete exposure information in the CRF. The drug diary will be returned to clinic staff at the end of each month.

Table 5-2. Regimen Description

Investigational Product	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Daratumumab	Pre-medication with corticosteroid, acetaminophen, diphenhydramine, and monteleukast 1-3 hours prior to administration (See section 5.1.1.3 for further details)	1800 mg	SC	D1, D8, D15, D22 for Cycle 1-2 D1, D15 Cycle 3-6 D1 Cycle 7 and onwards	Every 4 weeks
Azacitidine	Premedicate with antiemetics	75 mg/m^2 or MTD	IV/SubQ	Day -7 to Day -3 Cycle 1, Day 22-26 Cycle 1-3, Day 1-5 Cycle 5 and onwards	
Dexamethasone	Take prior to daratumumab administration on days of daratumumab administration and may also be given weekly on weeks without daratumumab	40 mg (or lower after Cycle 2)	PO	Dexamethasone 40 mg PO (or IV if PO is not available) weekly for Cycle 1 and 2. This dose may be reduced or stopped after Cycle 2 both on non-daratumumab administration weeks and on daratumumab administration weeks (as pre-medication). Further dose reduction is permitted based on dose modification criteria outlined in Section 5.5.	

See Dosing Schedule Diagram in Section 3.1.

5.3 Other Investigational Procedures/Modalities

There will be no other investigational procedures/modalities (e.g surgery, radiotherapy, hematopoietic stem cell transplantation) used in the protocol study treatment, if applicable.

5.4 Dose Limiting Toxicity

Dose-limiting toxicities are defined as the following toxicities if they occur anytime within the first 5 weeks of starting azacitidine (anytime within Cycle 1) and are thought to be secondary to azacitidine in combination with daratumumab:

- Grade 4 neutropenia lasting more than 7 days.
- Grade 4 thrombocytopenia lasting more than 7 days despite transfusion support.

- Grade 3 or higher non-hematological toxicity except:
  - Grade 3 nausea, vomiting or diarrhea that can be controlled within 48 hours with maximal supportive care.
  - Grade 3 hyperglycemia that can be controlled within 48 hours with appropriate supportive care.
  - Asymptomatic new Grade 3 or higher electrolyte disturbances that can be controlled with repletion or other medical management within 24 hours.

Severity of AEs will be graded according to CTCAE Version 5.0. As described in Section 8.2.2, interim analysis will occur after accrual of 6 patients in the safety cohort. Study accrual will be stopped until these 6 patients have completed at minimum 5 weeks of treatment after starting azacitidine (ie completed Cycle 1), at which point a formal interim safety analysis will be performed with assessment for DLTs as defined above and safety stopping bounds for DLTs as described in Section 8.2.2. Guidelines for dose reductions of azacitidine due to toxicity or dose delays/holding for daratumumab toxicity are detailed in Section 5.5.

5.5 Dose Modifications and Dosing Delays

Daratumumab

Dose Modification

No daratumumab dose modification (increase or decrease) will be permitted unless the subject's weight changes more than 10% from Cycle 1 Day 1 or the most recent weight used for dose calculation. Subject's weight will be recorded on all daratumumab dosing days.

Daratumumab-Related Toxicity Management and Dose Delay

ONLY if any of the following criteria are met and the event cannot be attributed to azacitidine, or underlying multiple myeloma, the daratumumab administration must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity (except for Grade 4 lymphopenia), or Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Grade 4 Neutropenia with any grade infection
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment within 48 hours of supportive care
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 48 hours of supportive care
  - Grade 3 fatigue or asthenia that was present at baseline and lasts for <7 days after the last administration of daratumumab
  - Grade 3 or 4 electrolyte disturbances which can be managed with replacement therapy

If daratumumab administration does not commence within the prespecified window of the scheduled administration date, then the dose will be considered a missed dose. See Table 5-3 Daratumumab-Related Dose Delay Time Chart.

Administration may resume at the next planned dosing date. See Section 5.5.1.4, Interruption or Missed Doses for additional information.

Table 5-3 Daratumumab-Related Dose Delay Time Chart

Weeks	Frequency	Missed Dose	Dosing Resumption
Weeks 1-8 (induction)	Weekly	≥3 days	Next planned weekly dosing date
Weeks 9-24 (consolidation)	Every 2 weeks	≥14 days	Next planned every 2 week dosing date
Week 25 onwards until disease progression (maintenance)	Every 4 weeks	≥ 14 days	Next planned every 4 week dosing date

A missed dose will not be made up. Any adverse event listed above deemed to be related to daratumumab that requires a dose hold of more than 3 doses will result permanent discontinuation of daratumumab and patient's withdrawal from this study.

Dose Delay

A dose is deemed to have been delayed if the treatment is 2-3 days beyond the theoretical day of treatment for weekly dose, 3-14 days beyond the theoretical day of treatment for Q2W dose, and 4-14 days beyond the theoretical day of treatment for Q4W dose. The reason for dose delay will be captured.

Interruption or Missed Doses

A daratumumab dose held for more than 3 days during induction, 14 days during consolidation, or 14 days during maintenance from the per protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Subjects who miss ≥3 consecutive planned doses of daratumumab for reasons other than toxicity will be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Azacitidine

Dose modification

The dose for azacitidine can be reduced as follows, based on counts for any given cycle:

Table 5-4 Dosage Adjustment for Azacitidine Based on Hematology Laboratory Values:

Counts		% Dose Administered in the Next Cycle
ANC (x 10^9/L)	Platelets (x10^9/L)	

<0.5 (Gr 4)	<25 (Gr 4)	50%
0.5 – 1.5 (Gr 2-3)	25-50 (Gr 3)	67%
> 1.5 (Gr 0-1)	> 50 (Gr 0 -2)	100%

Dosage Adjustment Based on Renal Function and Serum Electrolytes during treatment (not at baseline):
If unexplained reductions in serum bicarbonate levels to less than 20 mEq/L occur, the dosage should be reduced by 50% on the next cycle. Similarly, if unexplained elevations of BUN or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle.

Use in Geriatric Patients:
Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

For any other non-hematologic ≥ grade 3 AE thought to be secondary to azacitidine, dose should be held until recovery defined as improvement to at least grade 1, and resumed at 50% dose on the next treatment cycle. If non-hematologic ≥ grade 3 AE or hematologic ≥ grade 4 AE lasting more than 7 days thought to be secondary to azacitidine occurs at azacitidine dose < 25 mg/m^2, then azacitidine will be stopped and patient will withdraw from study. Guidelines for DLTs within the first cycle (ie within the first 5 weeks of starting azacitidine) are detailed in Section 5.4.

Further dose modifications or dose delays for azacitidine based on adverse events during treatment will be left to the discretion of the treating provider. In the event that the investigator feels deviation from the recommendations above is required, please consult the study chair to discuss for approval.

If the dose of azacitidine is reduced, at the investigator's discretion, the dose of azacitidine may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

Dose Delay

A dose is deemed to have been delayed if the treatment is ≥ 4 days beyond the theoretical day of treatment for this Q4W dose. The reason for dose delay will be captured.

Interruption or Missed Doses

An azacitidine dose held for more than 2 times for any reason other than toxicities suspected to be related to azacitidine will be reviewed by the study team at the earliest possible time. Subjects who miss ≥3 consecutive planned doses of azacitidine for reasons other than toxicity will be withdrawn from treatment. Any missed dose of azacitidine will not be made up.

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI CTCAE version 5.0.

If a participant experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

Table 5-5. Dose Modifications and Dosing Delays Tables for Specific Adverse Events

Dose modifications for AEs thought to be secondary to either drug, azacitidine or daratumumab, will be made as below:

Adverse Events: Neutropenia		
Grade of Event	**Management/Next Dose for Azacitidine**	**Management/Next Dose for Daratumumab**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Administer 67% of dose during next treatment course	No change in dose
Grade 3	Administer 67% of dose during next treatment course	No change in dose
Grade 4	Administer 50% of dose during next treatment course	Dose delay until recovery to at least Grade 1, can resume at same dose*
*Toxicity criteria for holding daratumumab dose are detailed above in Section 5.5.1.2 ** Participants having Grade 4 AE at azacitidine dose < 25 mg/m^2 should go off study		
Recommended management: • Use G-CSF as needed (except for Cycle 1 when it can only be used if patient develops ≥ Grade 3 neutropenia), start prophylactic antimicrobials and anti-fungals, and monitor closely for fevers and infection		
Adverse Events: Thrombocytopenia		
Grade of Event	**Management/Next Dose for Azacitidine**	**Management/Next Dose for Daratumumab**
≤ Grade 1	No change	No change
Grade 2	No change	No change
Grade 3	Administer 67% of dose during next treatment course	No change
Grade 4	Administer 50% of dose during next treatment course	Dose delay until recovery to at least Grade 1, can resume at same dose*
*Toxicity criteria for holding daratumumab dose are detailed above in Section 5.5.1.2 ** Participants having Grade 4 AE at azacitidine dose < 25 mg/m^2 should go off study		
Recommended management: - Transfuse platelets as needed and monitor for bleeding		
Adverse Events: Renal toxicity during treatment		
Grade of Event	**Management/Next Dose for Azacitidine**	**Management/Next Dose for Daratumumab**
≤ Grade 1	No change	No change

Adverse Events: Neutropenia		
Grade of Event	**Management/Next Dose for Azacitidine**	**Management/Next Dose for Daratumumab**
Grade 2	No change	No change
Grade 3	Hold dose until recovery to at least Grade 1, then resume dose at 50%	Dose delay until recovery to at least Grade 1, can resume at same dose*
Grade 4	Hold dose until recovery to at least Grade 1, then resume dose at 50%	Dose delay until recovery to at least Grade 1, can resume at same dose*
*Toxicity criteria for holding daratumumab dose are detailed above in Section 5.5.1.2 ** Participants having ≥ Grade 3 AE at a dose < 25 mg/m^2 should go off study		
Recommended management: - Hydrate with fluids, minimize other nephrotoxic agents, and monitor urine output		
Adverse Events: Other non-hematologic toxicity during treatment		
Grade of Event	**Management/Next Dose for Azacitidine**	**Management/Next Dose for Daratumumab**
≤ Grade 1	No change	No change
Grade 2	No change	No change
Grade 3	Hold dose until recovery to at least Grade 1, then resume dose at 50%	Dose delay until recovery to at least Grade 1, can resume at same dose*
Grade 4	Hold dose until recovery to at least Grade 1, then resume dose at 50%	Dose delay until recovery to at least Grade 1, can resume at same dose*
*Toxicity criteria for holding daratumumab dose are detailed above in Section 5.5.1.2 ** Participants having ≥ Grade 3 AE at a dose < 25 mg/m^2 should go off study		

Dexamethasone

Dexamethasone Toxicity

For management of dexamethasone toxicity see table below. If dexamethasone is permanently discontinued due to toxicity, pre- and post-administration doses administered on the day of daratumumab dosing may be given at the investigators' discretion. This table represents suggested dose modifications of dexamethasone, but physician discretion and clinical judgment should prevail.

Table 5-6

NCI-CTCAE Category	Toxicity	Dose Change
Gastrointestinal	Grade 1-2 dyspepsia, gastric, or duodenal ulcer, gastritis requiring medical management	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, decrease dexamethasone dose by 50%.
	≥Grade 3 requiring hospitalization or surgery	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue therapeutic dose of dexamethasone and do not resume.
Cardiovascular	≥Grade 3 edema limiting function and unresponsive to therapy or anasarca	Diuretics as needed and decrease dexamethasone dose by 25%. If edema persists despite above measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Neurology/ Psychiatric	≥Grade 2 interfering with function but not interfering with activities of daily living	Hold dexamethasone until symptoms adequately controlled. Restart at 50% of current dose. If symptoms persist despite above measure, discontinue dexamethasone and do not resume.
Musculoskeletal	≥Grade 2 muscle weakness symptomatic and interfering with function but not interfering with activities of daily living	Decrease dexamethasone dose by 25%. If weakness persists despite above measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Metabolic	≥Grade 3 hyperglycemia	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measure, decrease dose by 25% decrements until levels are satisfactory.

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Dexamethasone Toxicity Management Chart

5.6 Criteria for Permanent Discontinuation of Study Drug(s)

Subjects who are experiencing a clinical benefit should remain on study if possible, unless significant toxicity puts the subject at risk, routine noncompliance puts the study outcomes at risk, the subject withdraws consent, or one of the treatment discontinuation reasons referred to in Section 5.5 occurs.

5.7 Use of Concurrent/Concomitant Medications

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 5.9, Prohibited Therapies. The principal investigator must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Systemic use of the following concomitant medications will be collected in the CRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of next-line anticancer treatment, if earlier: growth factors, transfusions, anti-infective medications (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmic medications and other cardiac supportive therapy, anti-epileptic medications, centrally acting psychiatric medications, anti-histamines and other medications targeting post-administration systemic reactions, and any anticancer therapy (including radiation).

Recommended Therapies

Prophylaxis for Bacterial Infection

Prophylaxis for bacterial infections should be considered per institutional guidelines and treating physician preference, especially for subjects with a history of recurrent bacterial infections or severe hypogammaglobulinemia.

Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended unless contraindicated.

Prevention of Steroid Induced Gastritis

Dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines, for example proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H2 blockers (ranitidine or equivalent).

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 see Section 6.3

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.

Permitted Therapies

In addition, subjects are to receive full supportive care. The following medications and supportive therapies are examples of support therapies that may be used at any time during the study:

- Antiviral medications should be considered per institutional guidelines.
- Colony stimulating factors and erythropoietin may be used as needed at the discretion of the treating provider (except for Cycle 1 when they can only be used if patient develops ≥ Grade 3 neutropenia or ≥ Grade 3 anemia respectively rather than pre-emptively to avoid interference with DLT monitoring in Cycle 1)
- Transfusion of platelets and RBCs per institutional goals
- It is important to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed).
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.
- Intravenous immunoglobulin (IVIG) may be considered for subjects with recurrent infection related to hypogammaglobulinemia.
- Prophylactic antiemetics, with the exception of corticosteroids
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.

5.8 Dietary Restrictions

There are no specific dietary restrictions for study participants.

5.9 Prohibited Medications

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma is prohibited, including medications that target CD38, as well as medications used for other indications that have anti-myeloma properties (for example, interferon). Any non-study chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving azacitidine treatment.

Concomitant participation in an interventional clinical trial(s) or use of investigational agent(s) as well as medical devices is prohibited. Administration of commercially available agents with activity against or under investigation for multiple myeloma, including systemic corticosteroids (>10 mg prednisone per day or equivalent) (other than those given for IRRs as described in Section 5.1.1.3, Management of Injection-Related Reactions) should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease.

Typically, IV contrast is not used in CT scanning of subjects with secretory multiple myeloma because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

6 Study Procedures and Schedule of Events

The study-specific procedures and assessments are detailed in this section and outlined in the Study Procedures and Schedule of Events.

Screening assessments must be performed within 28 days prior to the first dose of investigational product, unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator.

All on-study visit procedures are allowed **a window of ± 7 days** unless indicated otherwise on Table 6.1. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

6.1 Study Calendar

Period/ Procedure	**Screening**	**Cycle 1[a] (Pre-Induction Phase)**	**Cycle 1-2[a] (Induction Phase)**				**Cycle 3[a] (Consolidation Phase)**				**Cycle 4[a] (Consolidation Phase)**				**Cycle 5-6[a] (Consolidation Phase)**				**Cycle 7[a] and Onwards (Maintenance Phase)**	**End of Treatment**	**Follow-up[t]**
Study Day/Visit Day	D -27 to D-8	D -7 to D-3	D1 (± 1 day)	D8 (± 1 day)	D15 (± 1 day)	D22 (± 1 day)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 3 days)		
Study Treatment/Drug																					
Daratumumab[b]			x	x	x	x	x		x		x		x		x		x		x		
Azacitidine[c]		x				x				x					x				x		
Dexamethasone[d]			x	x	x	x	x		x		x		x		x		x		x		
Administrative Procedures																					
Informed Consent	x																				
Clinical Evaluation																					
Physical Exam	x	x	x				x				x				x				x		
Medical History	x																				
Vital signs	x	x	x	x	x	x	x		x	x	x		x		x		x		x	x	
Weight/height[e]	x	x	x	x	x	x	x		x	x	x		x		x		x		x	x	
Concomitant medications	x	Continuously throughout study period																			
AE assessment[f]	x	Continuously throughout study period																			
Performance status[g]	x	x	x				x				x				x				x		
Laboratory Assessments																					
Pregnancy Test[h]	x		x				x				x				x				x	x	
Type and Screen[i]	x																				
Hepatitis B (HBV) Serology[j]	x																				
HBV DNA Testing[k]	x	Q12W during treatment for patients who meet criteria																		x	x
Blood	x	x	x	x	x	x	x		x	x	x		x		x		x		x	x	

Chemistry[l]																				
Hematology[m]	x	x	x	x	x	x	x		x	x	x		x		x		x		x	x	
Disease Evaluation[m]																					
Immunoglobulins[n]	x	x	x				x				x				x					x	
Serum M protein[o]	x	x	x				x				x				x					x	
sFLC[p]	x	x	x				x				x				x					x	
serum IFE[q]	x	x	x				x				x				x					x	
Urine M protein (24 hour urine)[r]	x																			x	
Skeletal Survey	Only as clinically indicated by standard of care																				
PET/CT/MRI	Only as clinically indicated by standard of care																				
Study Procedure/Correlative Studies																					
Bone Marrow Biopsy[s]	x		x																		

[a] **Cycle**: Every cycle is 28 days (except for Cycle 1 which extends from day -7 to day 28). The treatment window is ± 1 days for induction phase, ± 2 days for consolidation phase, ± 3 days for maintenance phase

[b] **Daratumumab**: Daratumumab dose scheduling, pre-medications, dose modification, and DLTs are detailed in Section 5.

[c] **Azacitidine**: Azacitidine dose scheduling, dose modification, and DLTs are detailed in Section 5. Azacitidine will be given for 5 consecutive days starting Cycle 1 day -7 to day -3, Cycle 1-2 Day 22 – 26, Cycle 5 and onwards Day 1-5

[d] **Dexamethasone**: Dexamethasone 40 mg PO (or IV if PO is not available) weekly for Cycle 1 and 2. This dose may be reduced or stopped after Cycle 2 on both non-daratumumab administration weeks and on daratumumab administration weeks (as premedication) based on investigator's discretion. Further dose reduction is permitted based on dose modification criteria outlined in Section 5.5.

[e] **Weight/height**: Height is required at screening/baseline only. Weight is required at screening and with every daratumumab and first day out of 5 consecutive days of azacitidine administration

[f] **AE assessment**: All AEs including adverse events of new onset as well as worsening signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. After the 30 days all ongoing related non-serious AEs, ongoing SAE, and new related AE/SAEs are to be followed up to resolution or stabilization.

[g] **Performance Status**: This will be measured by ECOG

[h] **Pregnancy Test**: Women of child bearing potential must have a negative serum pregnancy within 7 days prior to first study drug administration and D1 of every cycle of treatment starting Cycle 2 (does not need to be performed Cycle 1 Day 1) and at the EOT visit as part of standard of care.

[I] Type and Screen: Type and screen study must be done at the time of screening

[j] **Hepatitis B (HBV) Serology**: Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc).

[k] **HBV DNA Testing**: 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. For these patients, HBV DNA testing PCR must be done Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment.

[l] **Blood chemistry**: To be done at screening/baseline, then within 3 days prior to every daratumumab administration and cycle of azacitidine, at the EOT visit, and as clinically

indicated. Blood chemistry includes: SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphate, lactate dehydrogenase (LDH), sodium, potassium chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine, albumin, and total protein

[m] **Hematology**: To be done at screening/baseline and then within 3 days prior to every daratumumab administration and cycle of azacitidine, at the EOT visit, and as clinically indicated. Hematology includes hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts.

[n-r] **Disease evaluations**: All lab tests including M-protein quantification (serum and 24-hour urine), immunoglobulins (IgG, IgA, IgM), serum immunofixation, serum free light chains should be performed at screening/baseline. Serum M-protein quantification, immunoglobulins, serum immunofixation, and serum free light chains should also be performed on Cycle 1 D -7 (unless completed within 14 days of this day during screening phase) and every cycle on D1 starting Cycle 2 (Do not need to be performed Cycle 1 Day 1). If UPEP is positive at screening, then repeat UPEP can be done at investigator's discretion. All radiologic assessments are to be performed as clinically indicated and not required by the study. Response is assessed on the basis of clinical and laboratory findings on D1 of every cycle starting C2 prior to study drug administration, whenever disease progression is suspected (eg, symptomatic deterioration) and at the EOT visit. The availability of the results must not prevent the initiation of the next cycle. Response will be assessed against baseline values obtained during screening.

[s] **Bone Marrow Biopsy**: Bone marrow biopsy for correlative studies will be performed prior to C0, D-7 (within 14 days of first azacitidine dose) and again at C1, D1 (**or after completion of first 5 days of azacitidine and prior to first daratumumab administration**) and only as clinically indicated at time of progression (though not required by study)

[t] **Disease assessments during follow-up period**: are only required for patients with PR or better who have discontinued treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy. Patients will be followed every month for progression during this period. Disease assessments required every month include evaluation of serum M-protein, serum free light chains, and serum immunoglobulins. A bone skeletal survey and PET/CT/MRI are only required if clinically indicated to confirm response or progression according to IMWG criteria. Disease assessments are not required in the follow-up period by this study for patients who have discontinued treatment due to progression or once patients starts treatment with another anti-cancer therapy. For patients who are off study due to disease progression, they will receive a phone call at minimum per study every 4 weeks for one year post last study drug treatment to assess survival

6.2 Participant Registration

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All participants consented to the study will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.3 Schedule of Procedures and Observations

The Study Calendar summarizes the frequency and timing of study procedures and assessments applicable to this study.

Study assessments will be performed only after written informed consent is obtained. At each visit, study assessments should be completed before the administration of any treatment. All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions.

Throughout the study, subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Medical resource utilization data will be collected.

Pretreatment Period

Screening Assessments

The Screening procedures and assessments must be completed within 28 days of initiating study treatment, unless otherwise noted. The signed ICF must be obtained before any study-specific procedures are performed. The screening phase begins when the ICF is signed. During the screening phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed. Results of tests such as skeletal survey, radiologic tests (eg, MRI) to document baseline size of known or suspected extramedullary plasmacytomas; or chest X-rays) performed up to 6 weeks (42 days) before enrollment may be used if these tests have been performed as part of routine follow-up for the subject's disease. A bone marrow biopsy will need to be done within 14 days prior to first azacitidine dose.

- History and Physical Examination
  - Including Vital Signs, weight/height, concomitant meds, AE assessment, performance status
- Laboratory Assessments:
  - Pregnancy Test: women of child-bearing potential must have a negative serum pregnancy

test result within 7 days prior to first IMP administration
  - Type and screen must be done prior to first daratumumab administration
  - 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. HBV serology is not required at Screening 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 Study Calendar (Section 6.1) Where required by local law, the results of HBV testing may be reported to the local health authorities.
  - Blood Chemistry: SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase (AP), lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, corrected serum calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine, albumin and total protein
  - Hematology: hemoglobin, hematocrit, red blood cell (RBC), white blood cell (WBC) with differential, platelet count
- Adverse events/serious adverse events are to be reported from the signing of the informed consent
- Disease Assessment: (all lab assessments to be performed within 28 days and all radiologic assessments as clinically indicated prior to first azacitidine administration)
  - M-protein quantification (serum and 24-hr urine)
  - Serum IFE
  - Serum free light chain levels
  - Immunoglobulins: IgG, IgA, IgM,
  - Radiologic imaging (PET/CT/MRI scan) of plasmacytoma (medullary and extramedullary), if clinically indicated
  - Skeletal survey (X-ray; including skull, rachis, all long bones, pelvis and chest), if clinically indicated.
- Correlative study procedure: baseline bone marrow biopsy prior to first azacitidine dose (within 14 days prior to first dose of azacitidine)

Treatment Period

The same evaluations as performed at screening/baseline will be performed for each of the required evaluations. Disease evaluations will be performed every cycle.

Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of treatment cycle. Any patient with platelets >30,000/μL at the beginning of any cycle who develops platelets ≤ 20,000/μL at any point during cycle should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL. If Grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L.

Otherwise will plan to check complete blood count and chemistry panel with every daratumumab administration and every cycle of azacitidine.

Cycle 1 Day -7 to -3

- History and Physical Examination
- Weight
- Vital Signs*
- Performance Status (ECOG)
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (not required to be repeated if screening labs were performed within 3 days prior to first study drug administration),
  - Hematology (not required to be repeated if screening labs were performed within 3 days prior to first study drug administration),
- Disease assessment (not required to be repeated if screening labs were performed within 14 days prior to first study drug administration)
  - M-protein quantification (serum)
  - Serum free light chain levels
  - Immunoglobulin quantification
  - Serum IFE
- **Administration of azacitidine 75 mg/m^2***

*Occur daily Day -7 to -3 as clarified in footnote of table, while the other items only needed on Day -7

Cycle 1, Day 1

- Physical Examination
- Weight.
- Vital Signs.
- Performance Status (ECOG)
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (not required to be repeated at Cycle 1 if labs were performed within 3 days prior to first study drug administration),
  - Hematology (not required to be repeated at Cycle 1 if labs were performed within 3 days prior to first study drug administration)
- Correlative Study procedure: Bone Marrow Biopsy # 2 prior to daratumumab first dose
- **Administration of daratumumab 1800 mg subcutaneous**
- **Administration of dexamethasone 40 mg PO/IV (32 mg on Day 1, 4 mg on Day 2 and Day 3)**

Cycle 1, Day 8 (repeat same Cycle 1, Day 15, Cycle 2, Days 8 and 15, Cycles 3-6, Day 15)

- Weight.
- Vital Signs.
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (can be performed within 3 days of study drug administration),
  - Hematology (can be performed within 3 days of study drug administration),
- **Administration of daratumumab 1800 mg subcutaneous**
- **Administration of dexamethasone 40 mg PO/IV for Cycle 1 and Cycle 2 (can be reduced or stopped at discretion of treating provide for subsequent cycles)**

Cycle 1, Day 22 (repeat on Cycle 2, Day 22)

- Weight
- Vital Signs*
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (can be performed within 3 days of study drug administration),
  - Hematology (can be performed within 3 days of study drug administration),
- **Administration of azacitidine 75 mg/m^2 (or modified dose based on AEs)***
- **Administration of daratumumab 1800 mg subcutaneous**
- **Administration of dexamethasone 40 mg PO/IV**

*Occur daily Day 22- 26 as clarified in footnote of table, while the other items only needed on Day 22

Cycle 2, Day 1, (repeat on Cycle 3, Day 1 and Cycle 4, Day 1)

- Physical Examination
- Weight.
- Vital Signs.
- Performance Status (ECOG)
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (can be performed within 3 days prior to study drug administration),
  - Hematology (can be performed within 3 days prior to study drug administration)
  - Serum pregnancy test
- Disease assessment
  - M-protein quantification (serum) (can be performed within 3 days of study drug administration),
  - Serum free light chain levels (can be performed within 3 days of study drug

administration)
- Immunoglobulin quantification (can be performed within 3 days of study drug administration)
- Serum IFE

- **Administration of daratumumab 1800 mg subcutaneous**
- **Administration of dexamethasone 40 mg PO/IV for Cycle 2 (can be reduced or stopped at discretion of treating provide for subsequent cycles)**

Cycle 3, Day 22

- Weight
- Vital Signs*
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (can be performed within 3 days of study drug administration),
  - Hematology (can be performed within 3 days of study drug administration),
- **Administration of azacitidine 75 mg/m^2 (or modified dose based on AEs)***

*Occur daily Day 22- 26 as clarified in footnote of table, while the other items only needed on Day 22

Cycle 5, Day 1 (repeat on Day 1 of Cycle 6)

- Physical Examination
- Weight
- Vital Signs*
- Performance Status (ECOG)
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (can be performed within 3 days prior to study drug administration),
  - Hematology (can be performed within 3 days prior to study drug administration)
  - Serum pregnancy test
- Disease assessment
  - M-protein quantification (serum) (can be performed within 3 days of study drug administration),
  - Serum free light chain levels (can be performed within 3 days of study drug administration)

Immunoglobulin quantification (can be performed within 3 days of study drug
- administration)
- Serum IFE

- **Administration of azacitidine 75 mg/m^2 (or modified dose based on AEs)***
- **Administration of daratumumab 1800 mg subcutaneous**
- **Administration of dexamethasone at discretion of treating provider**

*Occur daily Day 1-5 as clarified in footnote of table, while the other items only needed on Day 1

Cycle 7, Day 1 (repeat on Day 1 of subsequent cycles)

- Physical Examination
- Weight
- Vital Signs*
- Performance Status (ECOG)
- AE/SAE assessment
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (can be performed within 3 days prior to study drug administration),
  - Hematology (can be performed within 3 days prior to study drug administration)
  - Serum pregnancy test
- Disease assessment
  - M-protein quantification (serum) (can be performed within 3 days of study drug administration),
  - Serum free light chain levels (can be performed within 3 days of study drug administration)

Immunoglobulin quantification (can be performed within 3 days of study drug
- administration)
- Serum IFE

- **Administration of azacitidine 75 mg/m^2 (or modified dose based on AEs)***
- **Administration of daratumumab 1800 mg subcutaneous**
- **Administration of dexamethasone at discretion of treating provider**

*Occur daily Day 1-5 as clarified in footnote of table, while the other items only needed on Day 1

End of Treatment

- Weight
- Vital Signs
- Concomitant medications
- Adverse events/serious adverse events
- Laboratory Assessments:
  - Serum Pregnancy Test
  - HBV DNA Test
  - Blood Chemistry
  - Hematology
- Disease Assessment:
  - M-protein quantification (serum and 24-hr urine)
  - Serum free light chain levels (sFLC)
  - Immunoglobulins: IgG, IgA, IgM,
  - Serum IFE

- Radiologic imaging (PET/CT/MRI scan) of plasmacytoma (medullary and extramedullary), if clinically indicated
- Skeletal survey (X-ray; including skull, rachis, all long bones, pelvis and chest), if clinically indicated.

Post-treatment/ Follow-Up

Each subject will be followed until 1 year after his/her last dose of study treatment, until death or withdrawal of consent for study participation, whichever occurs first. The end of study is defined as when all subjects have completed either at least 1 year of follow-up, or until death or withdrawal of consent for study participation, whichever occurs first.

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. For these patients, HBV DNA testing PCR must be done Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment.

After confirmed disease progression or the start of a new treatment for multiple myeloma, subjects will at minimum be contacted by telephone every 12 weeks for follow- up assessments (ie, other malignancies, next-line therapy, PD on next-line therapy, and survival, as applicable) until death, withdrawal of consent for study participation, or the end of the 1 year follow-up period, whichever occurs first. Following disease progression on the next-line therapy, subjects will only be followed for survival.

If the information on other malignancies, next-line therapy, PD on next-line therapy, and survival is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the CRF.

Investigators may recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF.

Subjects will be instructed that study drug (ie, daratumumab) will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

6.4 Correlative Studies

There will be two bone marrow biopsies performed for correlative studies. The first bone marrow biopsy will be performed within 14 days prior to the first azacitidine dose (during the screening phase) and the second bone marrow biopsy will be performed after completion of first 5 days of azacitidine treatment and prior to first dose of daratumumab treatment.

Refer to laboratory manual for specific specimen collection instructions. The correlative studies below and the analysis will be performed in batched samples. Samples will be retained and stored at the end of the study.

CD38 Expression Changes

Pharmacodynamic analysis of surface CD38 Expression on primary plasma cells (Secondary Objective)

Assessment of CD38 regulation with treatment of azacitidine in this study population is one of the secondary objectives of this study. Bone marrow (BM) samples will be collected as described above. BM mononuclear cells (MNCs) will be subject to ficol separation and stained with CD38-FITC, CD138-APC R700 and Propidium Iodide among other markers. Cells will be washed with PBS, resuspended in 5% FBS-PBS and analyzed by flow cytometry on BD Cytoflex. CS&T (Becton Dickinson) and Rainbow calibration beads (Spherotech) will be used to calibrate the instrument and fluorescence intensity of sequential samples. MFIs will be calculated on Flow Jo software. This will be done in Dr. Arun Wiita's laboratory. Please see Section 8.2.5.1 for further details on analysis.

Methylation Pattern Changes

Analysis of methylation pattern changes induced by Aza on primary plasma cells (Exploratory Objective, contingent upon funding)

Assessment of methylation of plasma cell whole genome and CD38 specific genome will be performed via whole genome reduced representation bisulfite sequencing in collaboration with Zymo Research. BM samples will be obtained before and after exposure to Aza and DNA will be extracted via the Quick DNA miniprep kit (Zymo Research). 200ng of genomic DNA will be bisulfite converted using EZ DNA Methylation-Gold Kit (Zymo Research). Subsequently, a region of the CD38 CpG island will be PCR amplified and cloned into the TOPO cloning vector (Life Technologies). Clones will be verified by PCR and 10 verified clones will be sequenced for analysis of CpG content and methylation levels.

Tumor Microenvironment Changes

Assessment of tumor microenvironment changes induced by Aza (Exploratory Objective, contingent upon funding)

Analysis of bone marrow microenvironment changes induced by Aza will be performed via CyTOF assay. BM samples will be obtained as described above and samples will be stained and processed in collaboration with Dr. Matthew Spitzer's laboratory. Dr. Matthew Spitzer is one of the leaders in cancer immunotherapy and his laboratory is part of the Cancer Immunotherapy Program (CIP) as well as the Parker Institute for Cancer Immunotherapy. The mass cytometry (CyTOF) experiments will be performed in Dr. Matt Spitzer's lab at UCSF. Dr. Matt Spitzer is one of the leading researchers in tumor immunology.

CyTOF assay enumerates ≥ 98% of peripheral immune cells with ≥4 positively identifying antigens among a reference panel of 33 antibodies to cover major cell subsets quantifying activation and immune checkpoint molecules in a single assay. Spitzer et al.[57] established a reference panel of 33 anti-human antibodies (see Appendix 4 for full list of antibodies) for mass cytometry that can easily be incorporated into routine immunophenotyping studies in the context of cancer immunotherapy. The selected target antigens are distributed broadly across immune cell types and thus ensure that all major immune cell lineages and various functional subsets can be identified robustly and unambiguously. Using automated analysis, we will be able to identify stratifying immune signatures and compare the immune signatures pre and post Aza treatment.

Mass cytometry workflow[57]:

Sample preparation
Cryopreserved bone marrow biopsy samples will be thawed into 10mL of cold cell culture medium (RPMI-1640 (life technologies), 10% FBS, 1x L-glutamine, 1x penicillin/streptomycin (Thermo Fisher))

supplemented with 20 U/ml sodium heparin and 0.025 U/ml benzonase (Sigma) and washed once (250 g, 4°C).

Cellular barcoding
Where indicated, samples will be barcoded and combined into a composite sample before surface staining. Barcoding will be performed employing either a palladium-based barcoding approach applicable to fixed cells or a live cell barcoding methodology involving antibodies against the surface molecules beta-2-microglobulin and a sodium-potassium pump (CD298) as described.

Viability staining
Cisplatin (Sigma) will be resuspended to 100mM in DMSO, pre-conditioned for 48 h at 37°C and stored at 20°C. Viability staining will be performed by resuspending the sample in 1mL of PBS and adding cisplatin to a final concentration of 500 nM, followed by incubation for 5 min at RT and washing with CSM. Where indicated, cells will be fixed with 1.6% PFA in PBS for 10 min at RT and washed twice with cell staining medium (CSM: PBS with 0.5% BSA and 0.02% sodium azide (all Sigma)) before staining. In case live cell barcoding is employed, viability assessment will be performed by substituting cisplatin with DCED-palladium (Sigma) and following the protocol
as described here.

Antibody staining
Cell-surface antibody master-mix (2x) will be prepared by adding appropriate dilutions of all cell-surface antibodies into 50 mL CSM per sample. If samples contained more than 3 x 10^6 cells, antibody volume (but not total CSM volume) will be increased accordingly (e.g., 2-fold for up to 6 x10^6 cells). The antibody master-mix will be then filtered through a prewetted 0.1 µm spin-column (Millipore) to remove antibody aggregates and 50 mL will be added to the sample resuspended in 50 mL of CSM. After incubation for 30 min at RT, cells will be washed once with CSM. For intracellular staining, cells will be fixed using the FoxP3 / transcription factor staining buffer set (Thermo Fisher Scientific) to fix for 1 h at RT. After fixation, samples will be washed once with CSM and once with 1x permeabilization buffer (Thermo Fisher Scientific) by centrifugation for 5 min, 600 g at 4°C. Intracellular antibody master-mix (2x) will be prepared analogously to the surface antibody mix by adding appropriate dilutions of all intracellular antibodies into 50 ul permeabilization buffer per sample. 50 mL of 2x antibody master mix will be added to the samples in 50 mL permeabilization buffer and incubated for 1 h at RT. Cells will be washed once with permeabilization buffer and once with CSM. Finally, samples will be resuspended in intercalation solution (1.6% PFA in PBS and 0.5 µM iridium-intercalator (Fluidigm)) for 20 min at RT or overnight at 4°C.

Data acquisition
Before acquisition, samples will be washed once in CSM and twice in ddH_2O and filtered through a cell strainer (Falcon). Cells will be then resuspended at 1 3 106 cells/mL in ddH_2O supplemented with 1x EQ four element calibration beads (Fluidigm) and acquired on a CyTOF2 mass cytometer (Fluidigm).

Flow cytometry
Bone marrow samples will be thawed as described above and subsequently treated with Fc blocking reagent (BioLegend) for 10 min at 4°C. Antibody cocktails will be then added for 30 min and incubated at 4°C. All samples will be washed with PBS containing BSA (0.5%), then fixed with 1.6% PFA for 10 min at RT. Finally, the samples will be washed and analyzed on an LSRII flow cytometer (BD Biosciences) equipped with 405, 488, 561, and 640nm lasers.

Quantification and statistical analysis from the CyTOF assay will be described in detail in Section 8.2.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy: Antitumor Effect – Hematologic Tumors

Disease response and progression will be based on assessments according to the IMWG Guidelines[55] as defined in Section 7.1.1, Response Categories. Daratumumab detection on serum IFE has been demonstrated in subjects treated with 16 mg/kg and may interfere with the traditional IMWG criteria of negative serum IFE for CR or sCR. To mitigate this interference, daratumumab-specific IFE testing will be performed as clinically indicated in patients with IgG Kappa myeloma. This daratumumab-specific IFE testing utilizes anti-idiotype antibody to bind daratumumab and confirm its interference on IFE (see laboratory manual). For all subjects on study with VGPR, a serum IFE positive for IgG Kappa, and a negative M-protein by SPEP, daratumumab-specific IFE testing will be performed as clinically indicated if CR is suspected, to confirm the presence or absence of daratumumab on IFE. In addition, in subjects with IgG Kappa myeloma and an M protein on SPEP of ≤0.2 g/dL, the daratumumab specific IFE testing will also be performed to determine whether the paraprotein identified on SPEP/IFE is monoclonal daratumumab or the subject's endogenous myeloma protein.

Response Categories

Disease evaluations by laboratory tests must be performed per the schedule noted in the Study Procedures and Schedule of Events. This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria presented in table below. For quantitative Ig, M-protein, and IFE measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory.

Table 7-1 International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or flow cytometry
Complete response (CR)[b]	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial response (VGPR)[b]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow PC percentage was ≥30%. In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD)[c]	Increase of 25% from lowest response value in any one of the following: Serum M-component (absolute increase must be ≥0.5 g/dL) Urine M-component (absolute increase must be ≥200 mg/24 hours) Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) Bone marrow PC percentage: the absolute percentage must be >10% Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) that can be attributed solely to the PC proliferative disorder
Relapse from CR	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis. Development of ≥5% plasma cells in the bone marrow. Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

FLC = free light chain; IMWG = International Myeloma Working Group; M-protein = monoclonal paraprotein; PC = plasma cell.
All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require documentation of no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

[b] Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.

[c] Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria.[55] In the IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875 mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177 mM/L)
6. Hyperviscosity

In some subjects, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

Measurement of Endpoints for Response

The primary endpoint for response in this study is ORR as best response by the end of the study treatment. ORR is defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) based on responses as assessed using the International Myeloma Working Group (IMWG) Uniform Response Criteria. Response evaluation will be performed on a monthly basis. Disease progression by paraprotein should be confirmed within the first 4 weeks after last assessment. DOR is defined as the time from the date of the first response to the date of subsequent PD or death due to PD, whichever happens earlier. In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date, the DOR will be censored at the date of the last valid assessment performed before the analysis cut-off date or date of initiation of new anticancer treatment, whichever is earlier. DOR is determined only for patients who have achieved a response of ≥PR. DOR will not be calculated for patients that do not achieve a response.

Assessment of Disease Progression or Response

Disease progression must be consistently documented using the criteria in table in Section 7.1.1. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline. Disease progression based on imaging, bone marrow plasma cell percentage, or hypercalcemia (not attributable to any other cause) do not need to be confirmed. Bone marrow biopsy to assess morphology (aspirate and biopsy) at the time of progression will be at the discretion of the individual provider and not required by the study.

For subjects who discontinue study treatment before disease progression, disease evaluations should continue to be performed as described every 4 weeks until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first.

Methods of Response Evaluation

Response evaluation will include:

- M-protein quantification (serum and 24-hr urine)
- Serum free light chain (FLC) levels
- Bone marrow biopsy/aspiration (not required)

Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples will be collected for serum quantitative Igs, serum and urine M-protein measurements, serum and urine IFE measurements, and serum FLC assay in screening phase (within 28 days of first azacitidine administration). If urine samples cannot be collected, then serum markers will be used alone. Serum quantitative immunoglobulins, serum M-protein measurements, serum IFE, and serum FLC assay will be performed on Cycle 1 Day -7 (prior to first azacitidine dose), unless screening disease evaluation labs were performed within 14 days prior to this first azacitidine administration, and every subsequent cycle on D1 starting cycle 2 (disease evaluation labs do not need to be repeated on Cycle 1 Day 1) until off study and at EOT.

Blood (and 24-hour urine, as determined by the treating physician) samples for disease evaluation will be collected until the development of confirmed disease progression. Progression of disease based on serum markers will need to be confirmed by at least 1 repeat investigation. Progression of disease based on urine markers does not need to be confirmed. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline.

For subjects with VGPR and suspected daratumumab interference (see Section 7.1.1, Response categories), reflex serum IFE using the anti-idiotype monoclonal antibody can be used as clinically indicated to confirm daratumumab migration on the IFE. Subjects that meet all other IMWG criteria for CR, and whose positive IFE is confirmed to be daratumumab, will be considered complete responders.

Bone Marrow Biopsy

Bone marrow biopsy will be performed on Cycle 1 Day -7 (or within 14 days prior) and Cycle 1 Day 1 (or after completion of first 5 days of azacitidine and prior to first daratumumab administration). Bone marrow biopsies to assess response or progression will not be required by the study but will be left to the discretion of the individual provider.

7.2 Evaluation of Safety

Safety will be measured by adverse events reported to the investigators by participants, laboratory test results, and clinical evaluation. Toxicity will be assessed according to the NCI CTCAE version 5.0. Safety analyses will be performed for all participants who have completed at least one dose of treatment and will encompass the duration of each participant's study treatment and until 30 days after last treatment. Please see Section 8.1.3 for further details on safety analysis.

Any clinically relevant toxicity ($\geq$ grade 3 hematologic adverse events or any grade non-hematologic adverse events) as determined by the treating provider thought to be probably, possibly, or definitely related to daratumumab, azacitidine, or dexamethasone exposure should be reported. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Overview

As the sponsor of the Study, Principal Investigator shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

Principal Investigator will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events, special situations including pregnancies and product quality complaints will be reported as described in this exhibit from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of a product under study within the study. All subsequent AEs and SAEs will be collected after this period if the Principal Investigator considers the AE/SAE to be causally-related to the use of the study drug.

For the purposes of this study, the J&J medicinal product is: DARZALEX® (daratumumab). The Celgene medicinal product is: VIDAZA™ (azacitidine).

7.3 Definitions of Adverse Events

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

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:

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

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

Serious Adverse Events (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.

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.]

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.

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, section 6, Reference Safety Information

7.4 Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

7.5 Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator, or until the initiation of new anti-cancer therapy, whichever occurs first. For selected adverse events for which administration of the investigational product was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the investigator.

7.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

Adverse events (with the exception of progression of multiple myeloma) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study (ie, from the time a signed and dated informed consent if obtained until 30 days following the last dose of study treatment).

7.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to Institutional Review Board

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

UCSF IRB website for guidance in reporting adverse events: https://irb.ucsf.edu/adverse-event

Expedited Reporting to the FDA

If the study is being conducted under an IND, the Sponsor (or the Sponsor-Investigator) is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with federal regulations (21 CFR §312.32).

The Sponsor (or Sponsor-Investigator) must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Interventional IIS Janssen Scientific Affairs Requirements for Safety Data Collection and Reporting

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
- Any failure of expected pharmacological action (i.e., lack of effect) of 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

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.**

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

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

Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by 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 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.

Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. 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.

Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for J&J 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 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.

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)

Principal Investigator will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a J&J product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 7.3, Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**
In the event the study is blinded, 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.

- 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 to Janssen Scientific Affairs, LLC using a transmission method in Section 7.4.4.9 within **24 hours of such report or correspondence being sent to applicable health authorities.**

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.

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 J&J medicinal product under study must be reported to Janssen Scientific Affairs, LLC by 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 J&J medicinal product under study is combined with either a serious adverse event or non-serious adverse event, 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.

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, 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.

Transmission Methods

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

- Electronically via J&J 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.

8 Statistical Considerations and Evaluation of Results

8.1 Sample Size Determination

This is a single-arm, open-label, 2-stage phase II study designed to evaluate the efficacy of daratumumab in combination with azacitidine and dexamethasone in RRMM patients previously treated with daratumumab. A Simon's two-stage design[58] will be used for this study. The study will begin with accrual of 6 patients in a safety run-in. Safety monitoring bounds for study termination based on DLTs are described in Section 8.2.2. If the safety stopping bounds are not met, study will continue to accrue more Stage I patients.

Sample size calculation was based on assessing the overall response rate (ORR) using Simon's minimax 2-stage design. Interim analysis for efficacy, using ORR, will be performed when the last patient enrolled to Stage 1 has received at least 2 cycles of treatment.

The overall target sample size of 23 patients is based upon having sufficient information to assess whether combined treatment of daratumumab with azacitidine and dexamethasone increases the ORR in this study population of RRMM patients with prior treatment with daratumumab. Data from ongoing clinical trial evaluating the safety, pharmacokinetics, and efficacy of isatuximab in patients with RRMM previously treated with daratumumab has shown preliminary results of ORR 8% (NCT02514668). Isatuximab is another CD38 monoclonal antibody with similar efficacy to daratumumab in RRMM patients.[24] Based on these previous results, for this study we would be interested in detecting an improvement in the ORR from a null rate of 8% to 33% ORR, which is based on the daratumumab-pomalidomide-dexamethasone

combination study in patients with RRMM re-treated with daratumumab.[23] Simon's minimax two-stage design will be used. The null hypothesis that the true response rate is 8% will be tested against a one-sided alternative that the true response rate is higher than 33%. In the first stage, 13 patients will be accrued. If there are 1 or fewer responses in these 13 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 23. The null hypothesis will be rejected if 5 or more responses are observed in 23 patients. The design will have a 90% power to reject the null hypothesis, if the true response rate is 33%, at one-sided 5% significance level. Accounting for an approximate 10% drop-out/ineligibility rate, maximum target accrual should not exceed 25 participants.

8.2 Analyses

Analyses Population

Analysis of primary and secondary efficacy variables will be based on the response-evaluable population, which includes all subjects who have measurable disease and received at least 2 cycles of study treatment, and have at least 2 efficacy evaluation assessments. All safety analyses for AEs will be based on the safety analysis set, which includes all subjects who receive at least 1 cycle of study treatment.

Safety Analysis

The study will begin with accrual of 6 patients in a safety run-in with interim safety analysis occurring after these 6 patients have completed at minimum Cycle 1 and further accrual stopped until safety analysis completed. If ≥ 2/6 patients in the safety cohort have dose limiting toxicities (DLTs) as defined in Section 5.4, then further study accrual will be halted until the study PI, co-investigators, and the DSMC can review the data, and determine whether the study should continue, be amended with a lower starting dose of azacitidine, or be closed to further accrual. Toxicities will be monitored throughout the study using CTCAE 5.0 criteria. Though we do not expect to observe DLTs during the study period, formal safety bounds based upon monitoring DLTs as defined in Section 5.4 will guide decisions about early stopping due to potential safety concerns. A Pocock-type sequential boundary[59] will be used to monitor dose-limiting toxicities with the aim of keeping the probability of early stopping at around 90% if the true underlying toxicity rate is 25%. If the number of dose-limiting toxicities is equal to or exceeds the stopping boundaries detailed in the following table at any point in the study, then accrual to the study will be suspended until the study PI, co-investigators, and the DSMC can review the data, and determine whether the study should continue, be amended with a lower starting dose of azacitidine, or be closed to further accrual. With a toxicity rate of 25%, the expected number of enrolled patients before stopping for excessive toxicities is 6.5.

Table 8-1. Table: Safety monitoring bounds for DLTs

Number of subjects	Stopping boundary
6-9	≥2
10-14	≥3
15-18	≥4
19-23	≥5

Adverse Events

Adverse events for safety analysis will be monitored for the duration of patient's treatment until 30 days post completion of treatment. The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the induction/consolidation or maintenance treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event. These will be provided using the same formats as those used for adverse events. At study conclusion frequency, proportion and severity of adverse events, and DLTs by dose level will be tabulated. Point estimates and confidence intervals will be calculated for all dichotomous endpoints.

Efficacy Analysis

Response to study treatment and progressive disease will be evaluated by the IMWG response criteria. [55]

Primary endpoints for efficacy

Primary endpoints for efficacy will be assessed by ORR. See Section 2.3 for definitions. To account for the adaptive nature of Simon's two-stage design, we will calculate the uniformly minimum-variance unbiased estimator, p-value and 95% CI for the response rates. The calculation will be performed using R *clinfun* package (www.r-project.org).

Secondary endpoints for efficacy

Secondary endpoints for efficacy will be assessed using duration of response (DOR), progression-free survival (PFS), and overall survival (OS). DOR is defined as the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the IMWG criteria or death due to PD whichever occurred first. DOR for subjects who have not progressed will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. PFS which is defined as the duration from the date of first dose of study treatment to the date of first documented evidence of progressive disease or death, whichever occurs first. Participants without a disease assessment will be censored at the date of first study treatment received. OS will be calculated as the time from the first dose of study treatment until death from any cause. Participants who have not died will be censored at the last time the participant was known to be alive. Distributions of DOR, PFS, and OS will be summarized using the Kaplan-Meier estimator. For each secondary efficacy endpoint, median even-free survival will be reported and the corresponding 95% confidence interval will be calculated using Brookmeyer and Crowley method.

Correlative Studies Analysis

CD38 regulation by azacitidine (Secondary Endpoint)

Change in CD38 surface expression in MM patients treated with azacitidine will be summarized using descriptive statistics and tested using the one-sample t-test. Two-sided p-value less than 0.05 will be considered statistically significant. The proportion of patients with at least a 1.5 fold increase in CD38 expression after one cycle of azacitidine treatment will also be reported. This phase II sample size of 23 will provide >99% statistical power to detect a fold change of 1.965 (SD: 0.299) in CD38 surface expression of MM patients treated with azacitidine based on a one-sample t-test at a two-sided type I error rate of 0.05. This estimated change in CD38 surface expression was calculated from our preliminary pre-clinical data. The association between the fold change in CD38 expression post azacitidine treatment and depth of response and duration of response will also be evaluated using logistic regression, linear regression methods, and Spearman's correlation coefficient, as appropriate.

DNA methylation pattern changes with azacitidine (Exploratory Objective, contingent upon funding)

Paired t-tests will be used to compare the DNA methylation levels between the samples pre and post Aza treatment. Analysis will be corrected for multiple hypothesis testing by controlling the false discovery rate (FDR). The distribution of uncorrected p values will be analyzed and an FDR will be inferred for each differentially methylated region (DMR). The inference will be made using the q value method available in R/Bioconductor. The dependence between statistical tests carried out for neighboring CpGs will be modeled to increase statistical power. Statistical comparisons will be carried out on larger genomic regions rather than single CpGs, such that neighbouring CpGs with similar differences in DNA methylation reinforce each other and give rise to more significant results. Hierarchical models will be used to minimize small standard deviations that frequently arise by chance. Standard deviation of a given CpG or genomic region will be estimated as the average of observed and expected values to obtain more robust P values for DNA methylation comparisons. A ranked list of DMRs will be established by incorporating p values as well as the relative and absolute differences in DNA methylation between samples pre and post Aza treatment.

Assessment of bone marrow tumor microenvironment changes (Exploratory Objective, contingent upon funding)

CyTOF will be used to report the changes in bone marrow tumor microenvironment before and after treatment with Aza, one of the exploratory endpoints of the study. Data generation and analysis will be done in collaboration with Dr. Matt Spitzer's laboratory at UCSF.

Data normalization and gating

After acquisition, data from acquired samples will be bead-normalized using MATLAB-based software. Barcoded cells will be assigned back to their initial samples using MATLAB-based debarcoding software. Normalized data will be then uploaded onto the Cytobank analysis platform to perform initial gating and population identification using the indicated gating schemes.

Data visualization and analysis

For further downstream analysis, pre-gated data will be imported into the R environment using the flowCore package. Data will be transformed with an inverse hyperbolic sine (arcsinh) transformation using a cofactor of 5 and normalized to the 99.5th percentile of each respective channel before downstream tSNE and Scaffold analysis. Visualization of samples by tSNE dimensionality reduction will be calculated using the Rtnse package with default parameters: perplexity = 30, theta = 0.5, max_iter = 1000 using the indicated

channels. To build a reference scaffold, bead and percentile-normalized data from live, CD45+, single, non-neutrophil cells will be imported into the statisticalScaffold package. All available channels will be used to build the reference maps. All population-relevant antigens will be included in the clustering analysis. Astrolabe analysis will be carried out by uploading bead-normalized data. Single-cell data will be clustered using the FlowSOM R package. Cell subset definitions follow. Cluster labeling method implementation, and visualization will be done through the Astrolabe Cytometry Platform (Astrolabe Diagnostics, Inc.).

Statistical analysis

In order to identify parameters of the immune system that are impacted by azacitidine treatment, we will use unbiased, unsupervised approaches that have been developed from mass cytometry (CyTOF) data. We will utilize an unsupervised clustering algorithm to identify immune cell subsets that is capable of handling large datasets and has been utilized previously for this purpose (clara, implemented in R, as in Spitzer et al.[3]). Changes in the abundance of each cluster will be evaluated using permutation-based statistical methods adapted previously for this purpose (SAM, implemented in R, as in Bruggner et al.,[4] Gaudilliere et al.,[5] Spitzer et al.[6]), which accommodate paired data (before and after) and handle multiple hypothesis testing. Immune cell subsets will be considered to change significantly when $q \leq 0.05$. We will evaluate both changes in immune cell abundances as well as changes in immune cell proliferation (% Ki-67+ cells) in this way. We will further evaluate significant results by manually identifying cell populations in the raw data by gating. These results will form the basis for the evaluation of a validation cohort in the future.

Visualization

Plots will be created using the ggplot2 R package. Schematic representations will be created with biorender (https://biorender.com/). Figures will be prepared in Illustrator (Adobe).

8.3 Interim Analyses and Study Stopping Rules

As described in Section 8.2.2, interim analysis will occur after accrual of 6 patients in the safety lead-in. Study accrual will be stopped until these 6 patients have completed at minimum cycle 1 of treatment, at which point a formal interim safety analysis will be performed with assessment for DLTs as defined in Section 5.4 and safety stopping bounds for DLTs as described in Section 8.2.2 and included again in the table below. If ≥2/6 patients have DLTs, then further accrual to the study will be suspended until the study PI, co-investigators, and the DSMC can review the data, and determine whether the study should continue, be amended with a lower starting dose of azacitidine, or be closed for further accrual. Otherwise, study will continue. Safety monitoring will continue for the remaining duration of the trial. A Pocock-type sequential boundary[59] will be used to monitor dose-limiting toxicities with the aim of keeping the probability of early stopping at around 90% if the true underlying toxicity rate is 25%. The accrual will be halted until further study investigation if excessive numbers of dose-limiting toxicities are observed, that is, if the number of dose-limiting toxicities is equal to or exceeds the stopping boundaries in the following table. With a toxicity rate of 25%, the expected number of enrolled patients before stopping for excessive toxicities is 6.5.

Table: Safety monitoring bounds for DLTs

Number of subjects	Stopping boundary
6-9	≥2
10-14	≥3
15-18	≥4
19-23	≥5

As described previously in Section 8.1, interim efficacy analysis will occur after completion of Simon's Stage I. 13 patients will be enrolled in Simon's Stage I. If there are 1 or fewer responses in these 13 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 23.

8.4 Accrual Estimates

There are around 1500 active myeloma patients being seen at UCSF. We would expect to accrue about 2-3 patients per month, which ideally would mean 8-12 months for patient accrual.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the PI will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to participants before any protocol related procedures are performed on any participants.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the FDA has determined that the study is exempt from IND requirements.

The PI must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB - approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC, IRB, and Janssen prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

9.5 Handling and Documentation of Clinical Supplies

The PI will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The PI shall not make the investigational drug available to any individuals other than to qualified study participants. Furthermore, the PI will not allow the investigational product to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The PI and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the PI will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the PI is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the PI and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

9.8 Record Keeping and Record Retention

The PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the PI shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all participants involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the participant’s rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Participants will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the participant’s medical records, and each participant will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Data and Safety Monitoring Plan

Data and Safety Monitoring Plan for a Phase II or III Institutional Trial

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Semiannual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.
All institutional Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance. Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.
Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.
UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines). The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC via report at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94143

Appendix 3 Prohibited Medications List

Drug	Trade name (if applicable)
adalimumab	Humira
baricitinib	Olumiant
BCG	TheraCys and TICE BCG
certolizumab	Cimzia
clozapine	Clozaril
deferiprone	Ferriprox
etanercept	Enbrel
fingolimod	Gilenya
golimumab	Simponi
infliximab	Remicade
leflunomide	Arava
natalizumab	Tysabri
Samarium sm 153 lexidronam	Quadramet
siponimod	Mayzent
Talimogene laherparepvec	Imlygic
teriflunomide	Aubagio
thalidomide	Thalomid
tofacitinib	Xeljanz

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