IRB Approved at
the Protocol Level
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TITLE: Daratumumab Infusion Acceleration

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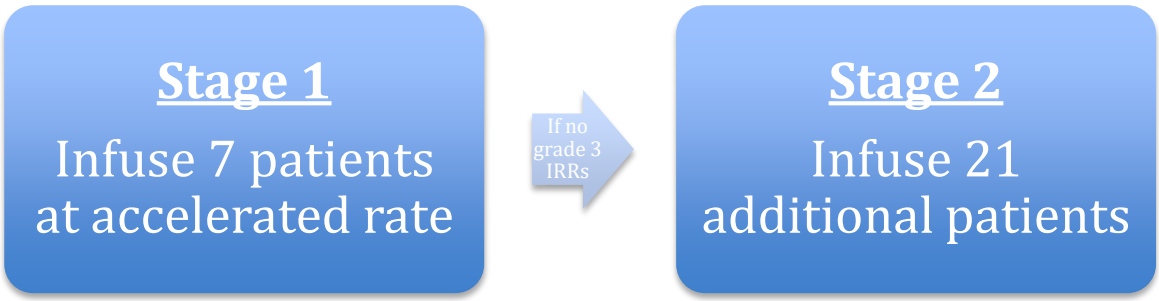
Commercial Agent: Daratumumab

Protocol / Version / Date: Original / v1.1 / 26-Aug-2016

SCHEMA

Title:	Daratumumab Infusion Acceleration
Objectives:	Determine the safety and tolerability of decreasing the infusion time of daratumumab in patients that have already received 2+ doses of daratumumab and are continuing on Daratumumab Estimate the time savings vs predicted infusion time
Population:	Any patient receiving daratumumab
Phase:	2
Number of sites:	1
Description of treatment :	Interventional unblinded Simon two-stage design of a faster Daratumumab infusion in patients who have received ≥ 2 infusions.
Study duration:	12-24 months
Participant duration:	Maximum 3 months



Starting with dose #3 or later of Daratumumab, we propose to infuse approximately 20% over 30 minutes, then 80% over 60 minutes, total duration of 1.5 hours, saving an estimated 2 hours.

Daratumumab Infusion Rates					
Dose	**Total Volume[1]**	**Initial Rate**	**Rate Increment**	**Max Rate**	**Time[2]**
Standard of care dose ≥ 3	550 mL	100 mL/hr	50 mL/hr every 1 hr	200 mL/hr	3.5 hr
Investigational dose ≥ 3	550 mL	200 mL/hr	30 minutes	450 mL/hr	1.5 hr

[1]Includes estimated overfill; [2]Estimated

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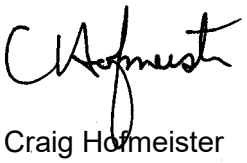
1. LIST OF ABBREVIATIONS

AE	Adverse event
BP	Blood pressure
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Investigational Review Board
IRR	Infusion Related Reaction
IV	Intravenous
NIH	National Institutes of Health
PI	Principal Investigator
PO	By mouth
RR	Respiratory rate
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
US	United States

2. STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training. I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal investigator: 

Craig Hofmeister

3. KEY ROLES

- **Hofmeister** – wrote the protocol, assisted with study design, assist with writing the manuscript; *planned* senior author

- **Barr** – conceived the idea, assisted with study design and protocol writing, consent the patients, enroll the patients, assist with tracking and entering data, assist with writing the manuscript; *planned* first author
- **Benson**, **Efebera**, **Rosko** – assist with writing the manuscript
- **Williams** & **Sharma** – assist with tracking and entering data, regulatory assistance regarding the clinical trial, assist with manuscript writing

4. OBJECTIVES

Hypothesis	Objective	Endpoint
Infusing daratumumab will not be associated with any grade 3-4 infusion related reactions	Determine the safety and tolerability of decreasing the infusion time of daratumumab in patients that have already received 2+ doses of daratumumab and are continuing on Daratumumab	Analysis of AEs possibly, probably, or definitely related to protocol therapy will summarize infusion related grade 3-4 reactions.
Accelerated daratumumab infusion will significantly decrease the time patients spend waiting for daratumumab to infuse.	Estimate the time savings vs predicted infusion time	The start and stop times of daratumumab infusion will be tracked during infusion acceleration and the number of daratumumab infusions will be tracked from the time of consent until the last daratumumab infusion.

5. BACKGROUND

5.1 Multiple myeloma

Multiple myeloma (MM) affects approximately 83,000 US citizens and over 50% of patients die within 5 years of diagnosis; more than half of patients older than 70 years with low albumin and high β2microglobulin die within a year of diagnosis[1, 2]. Of the 30,330 new cases estimated in 2016 in the U.S.[3], is twice as common in African Americans as Caucasians, and genetic changes accumulate as plasma cells degenerate from monoclonal gammopathy of undetermined significance, through smoldering myeloma, to MM[4]. MM is characterized by fractures, anemia, kidney failure, and hypercalcemia with a predisposition for bacterial infections from the inherent immunoparesis and varicella reactivation often aided by proteasome inhibition[5].

Patients have been treated with combinations of cereblon-binding drugs (e.g. immunomodulatory drugs [IMiD's] thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (e.g. bortezomib, carfilzomib), and dexamethasone. MM cells are strongly dependent on the BM microenvironment (*e.g.* bone marrow stromal cells,

endothelial cells, osteoclasts) via the production of supportive growth factors. Moreover MM cells are able to escape immune surveillance by creating an immunosuppressive BM microenvironment favorable to their survival.

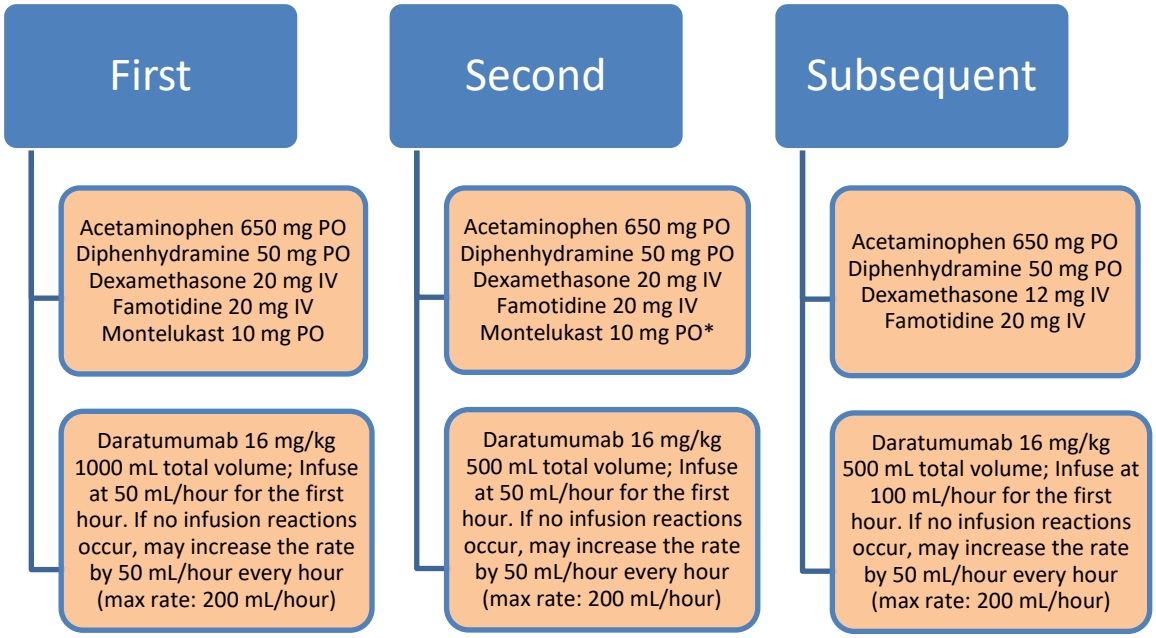
Two antibodies have received FDA approval in 2015 for relapsed refractory disease: elotuzumab (HuLuc63) is a humanized immunoglobulin (Ig)G1-k antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7, CS1 [CD2 Subset 1]), and daratumumab (HuMax-CD38) is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody that binds a CD38 epitope.

5.2 Rationale

In SIRIUS, after diphenhydramine 25-50 mg, acetaminophen 650-1000 mg, and methylprednisolone 100 mg intravenously, infusion-related reactions occurred in 45 (42%) patients and were predominantly grade 1 or 2 (grade 3 occurred in five [5%] patients). Thirty-seven percent of patients experienced infusion-related reactions during the first infusion and only six (6%) patients had more than one infusion-related reaction. The most common (≥5%) infusion-related reactions included nasal congestion (13 [12%]), throat irritation (seven [7%]), and cough, dyspnea, chills, and vomiting (six [6%] each). In the dose-escalation study[6], the frequency of infusion-related reactions was lower among patients who received 8 mg/kg in 1000 ml for 6 hours than among those who received 8 mg/kg in 500 mL for 4-6 hour or 16 mg/kg in 1000 mL for 6 hours, all suggesting that the infusion rate factors into infusion reactions. **All IRRs can be considered non-life threatening according to CTCAE grading system, most being nasal congestion.**

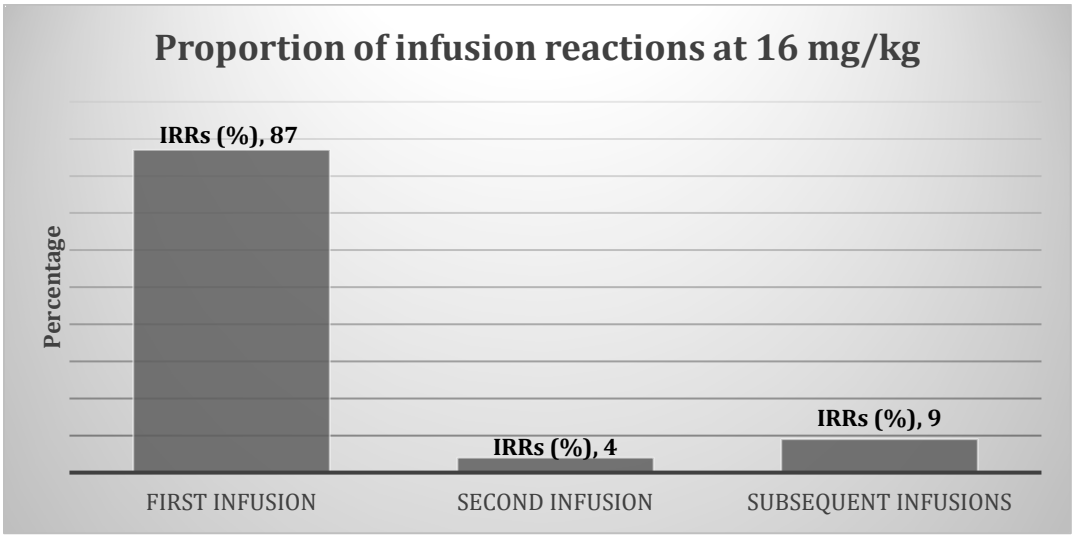
For patients receiving commercial daratumumab now, if a patient suffers grade 1-2 infusion reactions, we interrupt daratumumab. When symptoms resolve, we start at the last tolerated rate for one hour and begin re-escalating the infusion rate as tolerated. For grade 3 infusion reaction, we stop the infusion, treat medically, and restart at half the rate when symptoms improve to grade 0-1. The first dose of daratumumab should be diluted in one liter, but if this is well-tolerated, subsequent infusions can be diluted in 500 mL. Daratumumab is approved for 8 weekly infusions, 8 every other week infusions, and then monthly thereafter until progression. Our current institutional infusion recommendations for commercial daratumumab are shown below.

Daratumumab Infusions – Institution Standard



**Montelukast typically discontinued after dose #3.

This protocol focuses on dose #3 or later, when the risk of grade 3-4 infusion related reactions was very small in trials reported to date, as shown in the figure below.



6. PATIENT SELECTION

6.1 Eligibility criteria

6.1.1 Patients must have received ≥ 2 daratumumab infusions and be scheduled to receive another dose.

6.1.2 Both men and women of all races and ethnic groups are eligible for this study.

6.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of daratumumab in patients <18 years of age, children are excluded from this study.

6.1.4 Ability to understand and the willingness to sign a written informed consent document.

6.2 Exclusion Criteria

6.2.1 Any other medical condition, including mental illness or substance abuse, deemed by the principal investigator to likely interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.

6.2.2 Concurrent use of complementary or alternative medicines that in the opinion of the principal investigator would confound the interpretation of toxicities and/or antitumor activity of the study drug

6.2.3 Prisoner

7. REGISTRATION PROCEDURES

7.1 General Guidelines

Eligible patients will be entered on study at Ohio State University by Hallie Barr.

8. TREATMENT PLAN

8.1 Agent administration

Treatment will be administered on an outpatient basis.

Starting with dose #3 or later of daratumumab 16 mg/kg IV, we will infuse approximately 20% over 30 minutes, then 80% over 60 minutes, total duration of 1.5 hours, saving an estimated 2 hours. The initial rate will be 200 mL/hr (30 mins) and then 450 mL/hr (60 mins).

8.2 Premedication

The following premedications are recommended approximately 1 hour prior to daratumumab infusion per the package insert:

- Dexamethasone 12 - 20 mg IV/PO
- Diphenhydramine 25 - 50 mg IV/PO
- Acetaminophen 650 mg PO

The OSU institutional standard for infusion #3 and onward is

- Dexamethasone 12-20 mg IV/PO
- Famotidine 20 mg IV/PO
- Montelukast 10 mg PO (typically discontinued after dose #3)
- Consider acetaminophen 325-650 mg PO
- Consider diphenhydramine 12-25 mg IV/PO

If the premedication regimen has been adjusted due to prior tolerability or physician preference, the appropriateness of the premedication regimen will be evaluated by the study team.

8.3 Monitoring

Vital signs (HR, BP, temp, RR) will be taken just prior to infusion start, then every 15 minutes for the first hour of infusion, then lastly at the end of infusion (see Appendix B monitoring form). Patient will remain in the infusion clinic for a 30-minute post observation period after the first accelerated infusion *only*. If the infusion is well-tolerated, subsequent vital sign monitoring will occur prior to infusion start, at rate increase, and lastly at the end of infusion. Patients will be educated on the signs of

delayed infusion reaction and instructed to contact physician for any issues after discharge from clinic.

8.4 Duration of therapy

All further doses of daratumumab may be administered as described in section 8.1, however patient will be considered "off-study" after the pre-defined follow-up period.

8.5 Duration of follow-up

Patients will be followed for 4 weeks from the first accelerated infusion.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

8.6 Criteria for removal from study

If the patient suffers a grade 4 infusion reaction, the patient will be removed from the study.

9. DOSING DELAYS / DOSE MODIFICATIONS

Infusion reactions will be recorded as described in Appendix B.

9.1 Grade 1-2 infusion related reactions

At the time that this protocol was written, for daratumumab grade 1-2 infusion reactions, interrupt daratumumab. When symptoms resolve, start at the last tolerated rate for one hour and begin re-escalating the infusion rate as tolerated.

9.2 Grade 3 infusion related reaction

Follow institutional protocol. At the time that this protocol was written, for grade 3 infusion reactions, stop the infusion, treat medically, and restart at half the rate when symptoms improve to grade 0-1. Subsequent rate escalation is to occur at physician discretion.

9.3 Grade 4 infusion related reaction

Protocol accrual will be halted and the protocol modified.

10. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with daratumumab can be found in the FDA approved package inserts.

10.1 Daratumumab

Classification: fully human IgG1κ monoclonal antibody

Mode of Action: Daratumumab is an antibody directed against myeloma cell surface glycoprotein CD38 and inhibits tumor growth by 1) direct apoptosis through Fc mediated cross-linking and 2) immune-mediated cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP).

Administration: Per protocol, see section 8.1

Dosing: For treatment of myeloma, dose of daratumumab is 16 mg/kg IV, see prescribing information for dosing schedule. Dose is calculated based on actual body weight.

How supplied: Commercially

Preparation/Handling/Storage: Daratumumab will be prepared aseptically according to local procedures. See manufacturer package insert or institutional protocol for proper handling and storage of the medication.

10.2 Dexamethasone

Classification: Corticosteroid

Mode of Action: Dexamethasone is a synthetic adrenocortical steroid with potent anti-inflammatory effects in disorders of many organ systems. It decreases inflammation by suppression of neutrophil migration, decreased production or inflammatory mediators, and reversal of increased capillary permeability.

Administration: Administer the 4 mg/mL or 10 mg/mL intravenously as an undiluted or diluted solution. Oral tablets at an equivalent dose may be substituted for IV.

Dosing: Per treating physician.

How supplied: Commercially

Preparation/Handling/Storage: Dexamethasone will be prepared according to local procedures. See manufacturer package insert or institutional protocol for proper handling and storage of the medication.

11. STUDY CALENDARS

Patients will be approached in the infusion suite for consent, generally within 4 weeks of day 1. Screening and first infusion can occur on the same day.

11.1 SCHEDULE OF EVENTS

Assessment	Screening	First accelerated infusion
Signed informed consent	X	
Inclusion/Exclusion Criteria	X	
Height and weight[a]	X	
Vital signs	X	X
Daratumumab administration		X
Record adverse events		X

12. STATISTICAL CONSIDERATIONS

12.1 General approach

The primary objective of this study is to assess the safety of administering Daratumumab over a shortened period of time following the first two standard doses. The primary endpoint is infusion-related reactions (IRR) assessed with the first dose using the accelerated dosing regimen. The incidence rate of IRR is defined and calculated as the number of patients with grade 3 IRR divided by the total number of patients who receive the accelerated dosing regimen.

12.2 Safety analysis

Simon's two-stage optimal design was used to design the study. Two previous trials SIRIUS (n=106) and GEN501 (n=42) reported no grade 3 IRR with the 3rd or subsequent infusions. Given this observed proportion of 0/148, the upper bound of a 95% binomial confidence interval is 0.02, which translates to the alternative hypothesis that a desirable safety rate is at least 98%.

Based on previous clinical experience with daratumumab at our institution, 15% or higher incidence rate of grade 3 IRR is not acceptable, which leads to a null hypothesis that the true safety rate is at most 85%. With a type I error probability of 0.05 and 80% power, Simon's two-stage optimal design allows an interim analysis after 7 patients are enrolled. If only 6 or fewer patients are grade 3 IRR-free, we will conclude the regimen is not safe enough and trial accrual will be halted and the protocol modified. If all 7 patients are grade 3 IRR-free, we will continue to accrue to a total of 28 patients.

Out of all 28 patients, if the total grade 3 IRR-free patients is ≤26 (i.e. 2 or more patient with grade 3 IRR), we will conclude the regimen is too toxic. In addition, if any grade 4 IRR is observed, the trial will be suspended temporarily, and the regimen

will be reevaluated and modified to alleviate safety concerns. If the regimen is indeed too toxic with true safety rate no higher than 85%, we will have a 68% chance of early termination at the interim analysis.

With anticipated accrual rate of around 5-6 patients each month, the accrual period will be less than 6 months to achieve our 28 total enrollment goal.

12.3 Data safety monitoring plan

The data and safety monitoring plan will involve the evaluation of safety and data quality. Investigators will conduct review of data and patient safety at the regular myeloma census meetings (at least monthly). The PI of the trial will review reports of unexpected toxicities of the trial possibly, probably, or definitely related to Daratumumab infusion and determine if the risk/benefit ratio of the trial changes. Frequency and severity of related adverse events will be reviewed by the PI and compared to what is expected with Daratumumab infusion, including published literature and scientific meetings, to determine if the trial should be terminated before completion.
The study conduct will be reviewed by The Ohio State University – Comprehensive Cancer Center Data and Safety Monitoring Committee (DSMC). Any portion of the trial may be reviewed, but the DSMC will focus on unexpected toxicities possibly, probably, or definitely related to study intervention as well as the adequacy of the randomization of subjects.

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APPENDIX A - VERSIONS

Version	Date	Significant Revisions
	6-Aug -2016	Original
1.1	26-Sep-2016	Response to CSRC pharmacy stipulations. Some clerical updates

APPENDIX B – INFUSION RN DATA FORM

Assessment of hypersensitivity reactions and feasibility of an accelerated infusion Daratumumab protocol in patients with multiple myeloma. The following form will be entered into IHIS as a SmartPhrase.

Subject #_____

Date:_____

Infusion start time: _____

Daratumumab dose: _____

	Rate	BP	HR	Temp	RR	Comments
Initial						
15 min						
30 min						
45 min						
60 min						
EOI						

EOI = end of infusion

Medications Administered	**Description of Symptoms**	**Grade**
Time:		
Time:		
Time:		
Time:		

Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated

Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs

Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death

Adapted from: Common terminology criteria for adverse events (CTCAE): General disorders and administration site conditions. Version 4.03. June 14, 2010.

End time: _____