

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761036Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Darzalex (daratumumab)

Date: November 6, 2015

To: File for BLA 761036

From: John K. Leighton, PhD, DABT

Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting and labeling reviews for Darzalex conducted by Dr. Place, and secondary memorandum and labeling provided by Dr. Sheth. An addendum to the primary review was provided by Dr. Place that discusses the reproductive toxicology assessment regarding the risk of use of Darzalex in pregnancy. No relevant animal models are available for the testing of daratumumab; thus, the reproductive toxicology assessment relied upon information from CD38 knockout mice, expression of CD38 during embryo/fetal development, findings in cynomolgus monkeys where leukocyte antigens were targeted by monoclonal antibodies, and potential trans placental fetal exposure to daratumumab. The results of the assessment suggest that daratumumab exposure in the fetus may result in decreased bone density in infants and fetal myeloid or lymphoid cell depletion that is likely reversible as exposure to daratumumab declines. Drs. Place and Sheth concurred with this assessment. Labeling recommendations are provided in this addendum that reflects this assessment.

I concur with Dr. Sheth's conclusion that Darzalex may be approved for the proposed indication.

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/s/

JOHN K LEIGHTON
11/06/2015

MEMORANDUM

Date: November 05, 2015
From: Emily Place, PhD MPH
Pharmacology/Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
Addendum to Primary Review
BLA: 761036
Drug: Darzalex (daratumumab)
Indications: (b)(4) refractory multiple myeloma
Applicant: Millenium Pharmaceuticals, Inc.

This addendum summarizes the review of the scientific assessment submitted by the Applicant, regarding potential risks to reproduction and development resulting from exposure to daratumumab during and after pregnancy. The assessment was mainly based on information available in the scientific literature. Information relevant to the labeling for Darzalex is summarized below.

Developmental and reproductive toxicology assessment:

Daratumumab is a human IgG1 kappa monoclonal antibody that binds human CD38 and antagonizes its function. Daratumumab pharmacology includes a number of downstream immune-related mechanisms including complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), antibody-dependent cell phagocytosis (ADCP), apoptosis of CD38-expressing cells, and reduction of CD38 enzyme activity. Since the only pharmacologically relevant nonclinical species for daratumumab is the chimpanzee, in which reproductive and developmental toxicology studies are not feasible, a weight of evidence approach based on CD38 expression, potential embryo/fetal exposure, and knockout mouse data was used to inform Darzalex labeling. Evidence exists that CD38 is expressed in hematopoietic cells and tissues and in the bone, which are relevant to potential effects in the fetus and developing infants. Fetal exposure to daratumumab can occur due to placental transfer, and daratumumab could be present in a newborn where daratumumab levels would decline from the serum of infants in accordance with the elimination half-life of the antibody. Based on the mechanisms of action of daratumumab and findings in cynomolgus monkeys exposed to other monoclonal antibodies targeting human leukocyte antigens there is a potential for fetal myeloid or lymphoid-cell depletion. The Applicant also summarized the various phenotypes of CD38 knockout mice, which vary by strain of mice, and tabulated the types of effects observed in the immune system, pancreas, kidney, liver, pituitary, heart smooth muscle, bone, lung smooth muscle, and joint inflammation. Based on the information derived from the literature related to CD38 knockout mice, exposure to daratumumab during the fetal period could potentially result in decreased bone density in the infant. Adverse embryo-fetal effects would most likely be reversed as daratumumab exposure decreases.

The preceding information was incorporated into the Darzalex label as outlined below:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations [see Clinical Considerations]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

8.2 Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast fed child from DARZALEX or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

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/s/

EMILY J PLACE
11/05/2015

CHRISTOPHER M SHETH
11/05/2015

MEMORANDUM

Date: October 26, 2015
From: Christopher Sheth, PhD
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 761036
Drug: Darzalex (daratumumab) injection, for intravenous use
Indication: Treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent
Applicant: Janssen Biotech, Inc.

Daratumumab is an IgG1 κ human monoclonal antibody being developed as an intravenous infusion (16 mg/kg) for the treatment of patients with multiple myeloma. The antibody is directed against CD38, a protein expressed on the surface of a variety of cell types, with multiple functions including receptor mediated adhesion, signaling and enzymatic activity. The in vitro pharmacology studies submitted to the BLA indicate that daratumumab induces tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP) in malignancies expressing CD38.

Daratumumab was shown to cross-react to CD38 expressed in peripheral blood mononuclear cells from chimpanzees, but not with lymphoid tissue of cynomolgus and rhesus monkey, pig, rabbit, rat and mouse. The nonclinical toxicology data submitted to the BLA include a GLP 6-week study of daratumumab in chimpanzees and a nonGLP 2-week study with a surrogate anti-CD38 antibody HuMab-CD38 in cynomolgus monkeys. The primary toxicities identified in chimpanzees were infusion related reactions, thrombocytopenia, anemia, leukopenia, in addition to elevated AST values. The infusion reactions generally occurred after the first but not subsequent daratumumab infusions and the hematological and serum chemistry changes that were noted generally resolved during the recovery period. The prescribing information for Darzalex addresses the risks for infusion-related reactions and recommends premedication with corticosteroids, antipyretics and antihistamines. No chronic toxicity testing has been conducted with daratumumab. No genotoxicity studies were conducted with daratumumab (as per ICH S6) and no carcinogenicity were conducted with daratumumab (as per ICH S6 and S9). Due to the lack of pharmacologically relevant species, and because animal studies of fertility, early embryonic development and pre- and post-natal effect are not generally warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (as per ICH S9), these types of studies were not conducted with daratumumab.

The nonclinical studies needed to support product labeling were reviewed by Dr. Emily Place. The nonclinical findings are summarized in the “Executive Summary” of the BLA review and reflected in the product label. The Established Pharmacological Class of “human CD38-directed

monoclonal antibody” was determined to be both scientifically valid and clinically meaningful for daratumumab.

Recommendation: I concur with the pharmacology/toxicology reviewer that from a nonclinical perspective, Darzalex is recommended for approved, and that no additional nonclinical studies are needed to support approval of Darzalex in patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

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/s/

CHRISTOPHER M SHETH
10/26/2015

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 761036
Supporting documents: 3
Applicant's letter date: June 5, 2015
CDER stamp date: June 5, 2015
Product: Darzalex (daratumumab)
Indication: Darzalex is indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.
Applicant: Janssen Biotech, Inc.
Review Division: Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer: Emily Place PhD MPH
Supervisor/Team Leader: Chris Sheth PhD
Division Director: John Leighton PhD, DABT (DHOT)
Ann Farrell MD (DHP)
Project Manager: Jessica Boehmer MBA

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 761036 are owned by Janssen Biotech, Inc or are data for which Janssen Biotech, Inc has obtained a written right of reference. Any information or data necessary for approval of BLA 761036 Janssen Biotech, Inc does not own or

have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 761036.

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1 Executive Summary

1.1 Introduction

Daratumumab is a monoclonal antibody that binds to CD38 expressed on the surface of cells throughout the immune system including hematological malignancies. The drug will be administered at a recommended dose of 16 mg/kg as an intravenous infusion: weekly on Weeks 1 to 8; every two weeks from Weeks 9 to 24; and every four weeks from Week 25 onwards. Nonclinical pharmacology and toxicology studies have been submitted and reviewed to support the approval of Darzalex for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent.

1.2 Brief Discussion of Nonclinical Findings

According to the Applicant, daratumumab is designed to target CD38 positive B-cells and plasma cells and cause depletion of these cells via several effector-based mechanisms. CD38 is a 45 kDa type II transmembrane glycoprotein that has been described as both a receptor and a multifunctional enzyme involved in the production of nucleotide metabolites. CD38 is highly expressed in human hematopoietic cells/tissues, and at a lower level in pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells, and bone¹. Daratumumab (HuMax-CD38) bound to human and chimpanzee CD38, but it did not bind to CD38 from the mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Another anti-CD38 mAb, HuMab-CD38 or HuMab-3003-003, that binds human and cynomolgus monkey CD38 was also characterized and used in some exploratory studies.

In vitro pharmacology studies were generally conducted with one or more antibodies including daratumumab, HuMab-CD38, and/or the human isotype (negative) control antibody (HuMab-KLH). The in vitro studies demonstrated that daratumumab and HuMab-CD38 bound to purified human CD38 with high affinity as shown by K_D values in the low nanomolar (nM) range. Both antibodies also bound to several lymphoma cell lines. Daratumumab induced myeloma tumor cell lysis through complement-dependent cytotoxicity (CDC), whereas HuMab-CD38 has far less CDC activity. Daratumumab, HuMab-CD38 and rituximab were shown to elicit similar maximal lysis (approximately 40%) of lymphoma cells in vitro through antibody-dependent cell-mediated cytotoxicity (ADCC), and daratumumab is approximately twice as potent as either HuMab-CD38 or rituximab. Daratumumab and a variant (DARA-K322A) with an altered residue in the Fc region were shown to induce macrophage-mediated phagocytosis (antibody-dependent cellular phagocytosis (ADCP)) in malignancies expressing CD38. Daratumumab also promotes apoptosis through Fc mediated cross-linking, in vitro.

¹ Malvasi F et al., 2008. Evolution and Function in the ADP Ribosyl Cyclase/CD38 Gene Family in Physiology and Pathology. *Physiol Rev* 88:841-886.

Pharmacology studies also indicate daratumumab modulates CD38 enzyme activity through inhibition of ribosyl cyclase enzyme activity and stimulation of the cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of CD38, whereas the surrogate HuMab-CD38's ability to inhibit ribosyl cyclase enzyme activity is substrate dependent and it conversely inhibits cADPR hydrolase activity. Importantly, the degrees to which the known mechanisms contribute to the clinical efficacy of daratumumab is still unknown. In vivo pharmacology studies showed that daratumumab reduced tumor growth and burden in human lymphoma xenograft mouse models. Based on the nonclinical data submitted in the BLA and its chemical structure, the Established Pharmacological Class (EPC) of "human CD38-directed monoclonal antibody" was determined to be both clinically meaningful and scientifically valid for Darzalex (daratumumab).

Stand-alone safety pharmacology studies were not conducted with daratumumab. ECG parameters, respiratory rates, body temperatures and pulse rates were assessed during the 6-week repeat-dose toxicology study in chimpanzees and were unremarkable at doses up to 25 mg/kg. ECGs, body temperature and heart rate were assessed during the 2 week repeat dose toxicology study in monkeys and were unremarkable at doses up to 100 mg/kg.

The toxicology data for daratumumab was generated in the chimpanzee (in study that was not designed to be terminal and was not requested by the FDA), and in the monkey using the HuMab-CD38 surrogate antibody. These studies indicated there are no gender differences in exposure in chimpanzees or monkeys. Increases in C_{max} and AUC values are greater than dose proportional in the chimpanzee, and approximately dose proportional in monkeys. Daratumumab was slowly eliminated in the blood following intravenous dosing with half-lives of approximately 15.5 to 18.8 days in chimpanzees, and 9 to 63 hours for HuMab-CD38 in the monkey.

The general toxicology studies reviewed were a 6-week repeat-dose toxicity study in chimpanzee and a 2-week repeat dose toxicity study in the monkey. Both repeat-dose toxicity studies utilized IV dosing, which is the intended route of administration for Darzalex. In animals, daratumumab was found to target the hematopoietic and lymphatic systems, in addition to the liver and spinal cord and nervous system.

Findings include:

- Hematopoietic and lymphatic systems: Increases in red blood cells, hemoglobin, and hematocrit; decreases in white blood cells and platelets (chimpanzee and monkey); lymphoid depletion/atrophy in thymus, mandibular and mesenteric lymph nodes, spleen and peyers patch (monkey only).
- Liver: Elevated AST, ALT (chimpanzee only).
- Cytokine response reaction (chimpanzees only): Clinical signs include dyspnea, sneezing, increased mucous production, evacuation of bowels, mucous membrane pallor, diarrhea, soft stool, reduced appetite, respiratory arrest, and subsequent cardiac arrest leading to one mortality.

- Spinal cord and nervous system (monkey only): Spinal cord myelitis and inflammatory cell infiltrates found in spinal cord and sciatic nerves in recovery animals.

The Applicant did not conduct genotoxicity, reproductive and developmental toxicology studies, or carcinogenicity studies with daratumumab. Standard genotoxicity studies are not generally applicable to biotechnology-derived pharmaceuticals (per ICH S6) and were not needed. The considerations led to no reproductive and developmental toxicology studies being conducted for daratumumab include: the lack of a pharmacologically relevant species for testing (aside from the chimpanzee wherein these studies are not feasible); that these studies are not warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (per ICH S9). ICH S9 also outlines that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, and as such no carcinogenicity studies were needed.

1.3 Recommendations

1.3.1 Approvability

Recommended for approval. The nonclinical studies submitted to this BLA provide sufficient information to support the use of Darzalex for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The content for the labeling of daratumumab is contained in this review. Based on the nonclinical data submitted in the BLA, the Established Pharmacological Class (EPC) of “human CD38-directed monoclonal antibody” was determined to be both clinically meaningful and scientifically valid for daratumumab.

2 Drug Information

2.1 Drug

CAS Registry Number: 945721-28-8

Generic Name: N/A

Code Name: JNJ-54767414, HuMax-CD38

Chemical Name: Immunoglobulin G1-kappa, anti-
(CD3

(b) (4)

(b) (4)

(b) (4)

Molecular Formula/Molecular Weight: $C_{6466}H_{9996}N_{1724}O_{2010}S_{42}$; 148,300 g/mol (148kDa)

Structure or Biochemical Description:

Figure 1. Amino acid sequence of daratumumab

(b) (4)

Pharmacologic Class: human CD38-directed monoclonal antibody

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 100638 was submitted on 18 October 2007 for the first in human Phase 1 clinical trial of multiple myeloma (MM) patients who are (b) (4) refractory to at least 2 different established therapies.

2.3 Drug Formulation

Table 1. Darzalex drug formulation

Table 1: Composition of 100 mg Daratumumab DP

Component ^a	Grade	Function	Nominal Amount per Vial (5 mL)	Concentration
daratumumab	Company Standard	Active	100 mg	20 mg/mL
Glacial acetic acid	Ph. Eur./USP/JP	(b) (4)	0.9 mg	25 mM ^b
Sodium acetate trihydrate	Ph. Eur./USP/JP		14.8 mg	
Sodium chloride	Ph. Eur./USP/JP		17.5 mg	60 mM
Mannitol	Ph. Eur./USP/JP		127.5 mg	140 mM ^c
Polysorbate 20	Ph. Eur./NF/JPE		2.0 mg	0.4 mg/mL ^d
Water for injection	Ph. Eur./USP/JP		q.s.	q.s.
(b) (4)				

q.s. = sufficient quantity

2.4 Comments on Novel Excipients

There are no Pharmacology/Toxicology concerns with the excipients or their levels in the Darzalex drug product formulation.

2.5 Comments on Impurities/Degradants of Concern

N/A – Division of Therapeutic Proteins

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for Darzalex is patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory. The proposed dosing is 16 mg/kg body weight administered as an IV infusion according to the following dosing schedule:

Table 2. Proposed Daralex dosing schedule

Schedule	Weeks
Weekly	Weeks 1 to 8
Every two weeks	Weeks 9 to 24
Every four weeks	Week 25 onwards until disease progression

The drug will be provided for injection in single use vials at either 100 mg/5 mL or 400 mg/20 mL strengths.

2.7 Regulatory Background

NDA 761036 was submitted on June 5, 2015 for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent or are double refractory to a PI and an immunomodulatory agent.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	Study No.	Module
Primary Pharmacodynamics		
<i>In vitro Pharmacology</i>		
Binding of HuMax-CD38 and HuMab-3003-003 to human CD38	GMB3003-002	4.2.1.1
Induction of complement dependent cytotoxicity of CD38-specific antibodies daratumumab and HuMab-CD38	GMB3003-003	4.2.1.1
Antibody-dependent cell mediated cytotoxicity mediated by HuMab-CD38 and daratumumab	GMB3003-004	4.2.1.1
Antibody-mediated phagocytosis contributes to the anti-tumor activity of daratumumab in lymphoma and multiple myeloma	GMB3003-115	4.2.1.1
Capacity of daratumumab and HuMab-CD38 to inhibit CD38 enzyme activity	GMB3003-013	4.2.1.1
Induction of B cell apoptosis by daratumumab and HuMab-CD38	GMB3003-011	4.2.1.1
Daratumumab induces programmed cell death in vitro and in vivo via Fc gamma receptor mediated crosslinking	GMB3003-116	4.2.1.1
Binding of HuMab-3003-003 and HuMax-CD38 to cynomolgus monkey and human blood cells	SR3003-06-31	4.2.1.1
Binding of daratumumab to chimpanzee and human platelets at 4°C and at room temperature	BKV00015	4.2.1.1
Antibody induced complement mediated lysis of human erythrocytes	SR3003-06-67	4.2.1.1
Studies on the capacity of daratumumab to mediate proliferation and cytokine release of human blood cells: ex vivo treatment of whole blood samples and isolated PBMCs	GMB3003-018	4.2.1.1
<i>In vivo Pharmacology</i>		
Assessment of minimal HuMax-CD38 dose required to inhibit outgrowth of a xenograft of human lymphoma cells in SCID mice, using optical imaging	GMB3003-017	4.2.1.1
Repeat dose toxicology: (including supportive toxicokinetics)		
HuMax-CD38 Multiple Dose Safety Study in Chimpanzees with a 2-month Recovery Period	8754-0701	4.2.3.2
HuMab-CD38 (clone 3003-003): Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period	509808	4.2.3.2

3.2 Studies Not Reviewed

Study Title	Study No.	Module
Pharmacology		
<i>In vitro Pharmacology</i>		
Binding epitopes of daratumumab and HuMab-CD38	GMB3003-008	4.2.2.1
Studies on possible agonistic effects of daratumumab and HuMab-CD38 on proliferation, IL-6 and IFN γ production by human PBMCs	GMB3003-012	4.2.2.1
Investigation of the potential agonistic effect of HuMax-CD38 on cytokine release by human PBMCs	GMB3003-016	4.2.2.1
Capacity of daratumumab to mediate cytokine release of ex vivo treated human blood cells	GMB3003-020	4.2.2.1
Immunohistochemical analysis of binding of HuMab-CD38 and daratumumab to human lymphoid and non-lymphoid tissue	GMB3003-006	4.2.2.1
Immunohistochemical analysis of binding of HuMab-CD38 and daratumumab to lymphoid tissue of various species	GMB3003-010	4.2.2.1
Examination of cynomolgus and rhesus monkey cross reactivity of daratumumab and HuMab-CD38	GMB3003-005	4.2.2.1
Comparison of human and chimpanzee CD38 and interaction with daratumumab	GMB3003-014	4.2.2.1
Cross-reactivity of daratumumab to PBMCs from chimpanzees	BKV00001	4.2.2.1
Binding of daratumumab to chimpanzee and human PBMCs	BKV00013	4.2.2.1
Ex vivo evaluation of a combination treatment of MM cells with lenalidomide and the human CD38 mAb daratumumab	GMB3003-069	4.2.2.1
Evaluation of a combination treatment of newly emerging multi-drug therapies for MM with daratumumab in MM cells ex vivo	GMB3003-070	4.2.2.1
<i>In vivo pharmacology</i>		4.2.2.1
In vivo dose finding: Assessment of minimal HuMax-CD38 dose required to inhibit outgrowth of a xenograft of human lymphoma cells in SCID mice, using optical imaging	GMB3003-017	4.2.2.1
Pharmacokinetics		
<i>Analytical Methods and Validation Reports</i>		
Development and Validation of an ELISA method to detect HuMab-CD38 in cynomolgus monkey serum	259435	4.2.2.1
Development and Validation of an ELISA method to detect Cynomolgus antibodies to HuMab-CD38	259477	4.2.2.1
Transfer of ELISA methodology to determine concentrations of F(ab') ₂ fragments in chimpanzee serum samples	Bkv00005	4.2.2.1
Validation of an ELISA method for the determination of HuMax-CD38 in chimpanzee serum samples	Bkv00009	4.2.2.1
Toxicology		
<i>Other toxicity studies</i>		
HuMax-CD38-FITC an Immunohistochemical investigation of cross reactivity in a range of human tissues	260571	4.2.3.7.7
HuMab-CD38-FITC an Immunohistochemical investigation of cross reactivity in a range of cynomolgus monkey tissues	510574	4.2.3.7.7
Tissue Cross-Reactivity of FITC-labeled HuMax-CD38 with chimpanzee tissues ex vivo	Bkv00003	4.2.3.7.7

3.3 Previous Reviews Referenced

Nonclinical review of IND100638

4 Pharmacology

4.1 Primary Pharmacology

Daratumumab binding to CD38 in vitro

Study no: GMB3003-002

Methods

The binding of daratumumab to purified human CD38 was assessed using Biacore technology. Affinity determinations and binding kinetics were determined to calculate dissociation constants and make K_D determinations. ELISA assays confirmed binding in a concentration dependent manner.

Results

The calculated K_D value for daratumumab binding to purified human CD38 was 4.36 nM (Table 3). The K_D for binding of HuMab-CD38 surrogate antibody (HuMab 3003-003) to purified human CD38 was 0.818 nM. ELISA assays showed both daratumumab and HuMab-CD38 bound human CD38 in a concentration-dependent manner (Figure 2, 3). The EC_{50} of daratumumab binding to human CD38 was determined by ELISA using His-CD38 coated plates at 55.2 ng/mL (Figure 3).

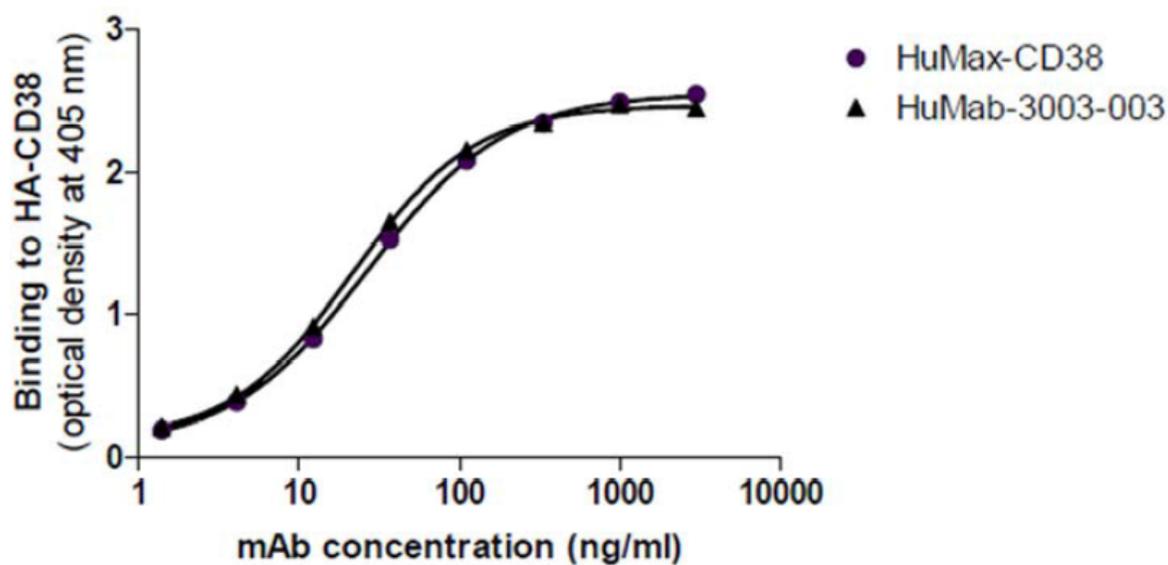
Table 3. Affinity measurements for daratumumab and HuMab-CD38

Sample	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (M)
Daratumumab	$1.24 \times 10^5 \pm 3.33 \times 10^4$	$5.08 \times 10^{-4} \pm 7.51 \times 10^{-5}$	$4.36 \times 10^{-9} \pm 1.47 \times 10^{-9}$
HuMab-CD38	$2.71 \times 10^5 \pm 1.23 \times 10^5$	$2.00 \times 10^{-4} \pm 1.63 \times 10^{-5}$	$8.18 \times 10^{-10} \pm 2.61 \times 10^{-10}$

^a Values expressed as mean \pm SD.

k_a = association constant or on rate; k_d = dissociation constant or off rate; K_D = equilibrium dissociation constant/affinity constant; SD = standard deviation

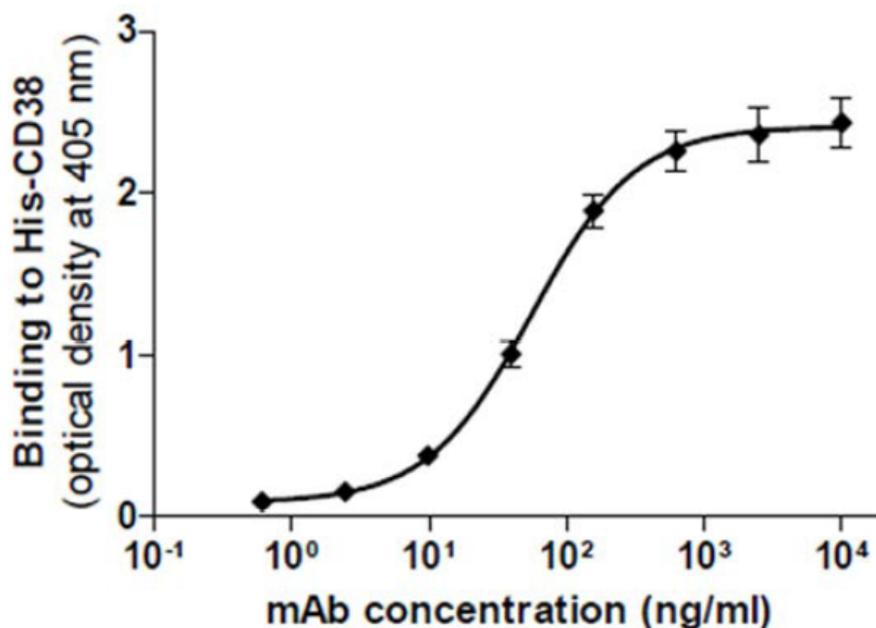
(Excerpted from the submission)

Figure 2. Concentration dependent binding of daratumumab and HuMab-CD38 binding to CD38 by ELISA

(Excerpted from the submission)

(Excerpted from the submission)

Figure 3. Concentration dependent binding of daratumumab to human CD38 by ELISA



(Excerpted from the submission)

Daratumumab binding to lymphoma and multiple myeloma cells

Study no: GMB3003-002

Methods

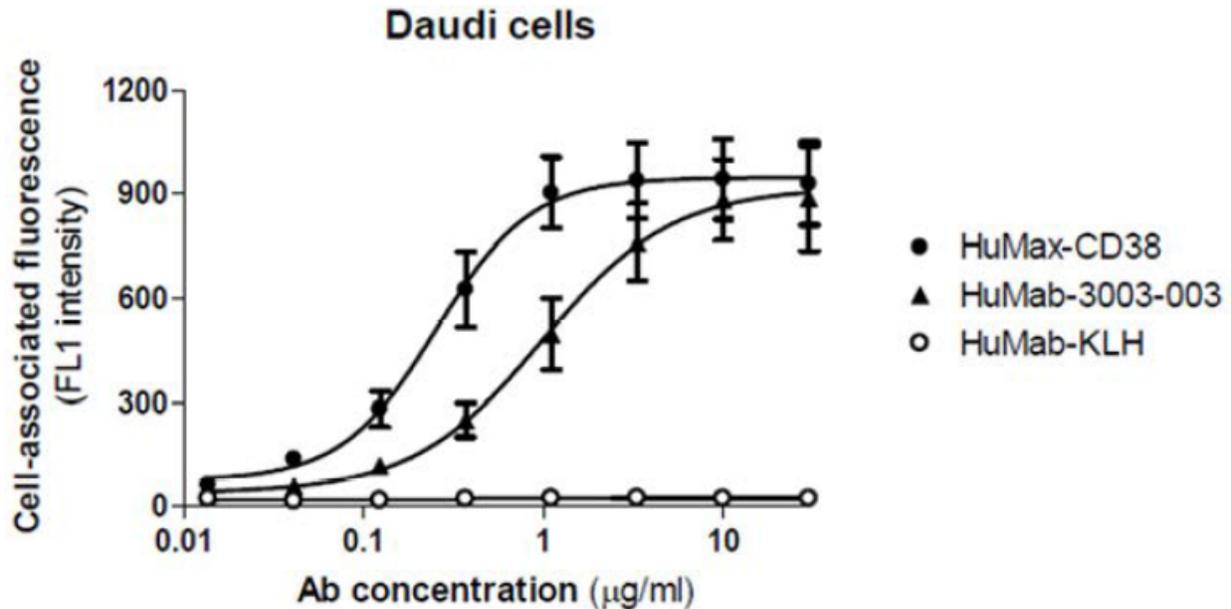
Binding of daratumumab (HuMax-CD38) and surrogate antibody Hu-Mab CD38 (HuMab 3003-003) to various lymphoma cell lines (Daudi, CHO) in vitro was conducted using flow cytometry (Figure 4, 5 respectively). Additionally six multiple myeloma derived cell lines and multiple myeloma cells derived from seven patients ex vivo were tested for specific concentration-dependent binding to daratumumab and Hu-Mab CD38 by flow cytometry. The EC₅₀ is the concentration of antibody that results in approximately 50% response, specifically binding to CD38 expressing target cells in these experiments.

Results

The EC₅₀ values determined were 0.26 and 0.47 µg/mL for binding daratumumab and 0.99 and 0.96 µg/mL for binding HuMab-CD38 (HuMab 3003-003) to Daudi and CHO-CD38 expressing lymphoma cells, respectively (Table 4). Binding on multiple myeloma cell lines was concentration-dependent but varied due to differences in CD38 expression among the cell lines. The EC₅₀ for daratumumab was 0.89 µg/mL in RPMI8226 cells and the EC₅₀ was 4.86µg/mL for HuMab-CD38. In all patient samples examined ex-vivo, there was a concentration-dependent increase in daratumumab

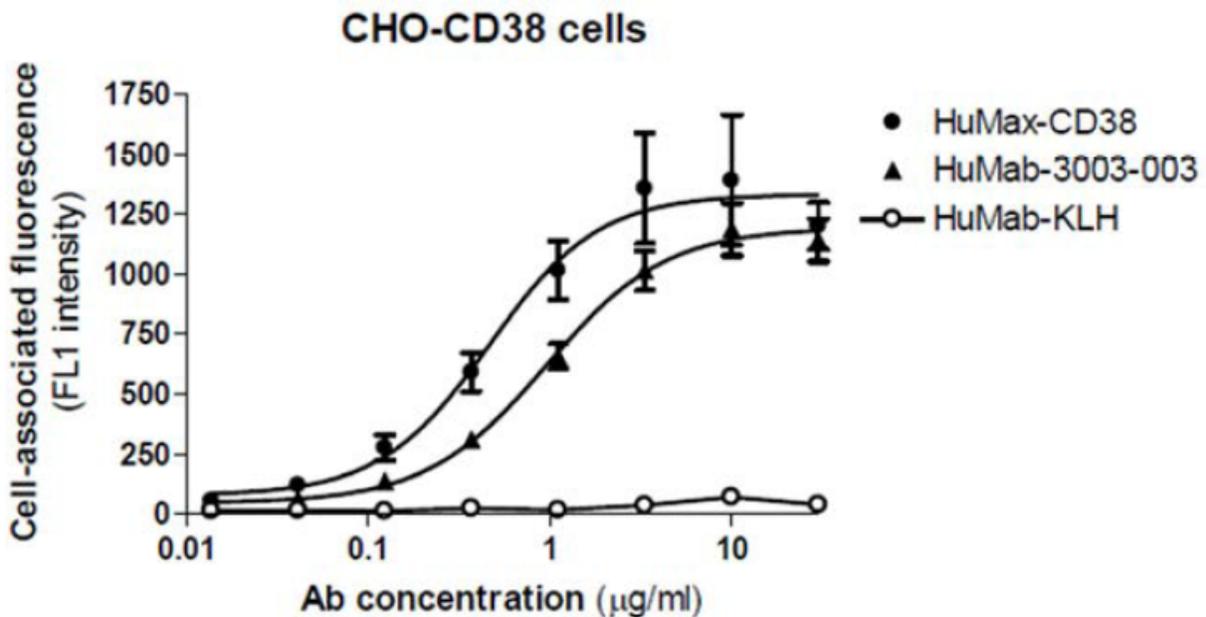
binding to multiple myeloma cells. The same was observed for HuMab-CD38; however, staining was less intense (Figure 6) as measured by flow cytometry.

Figure 4. Daratumumab binding to CD38 on Daudi lymphoma cells in vitro

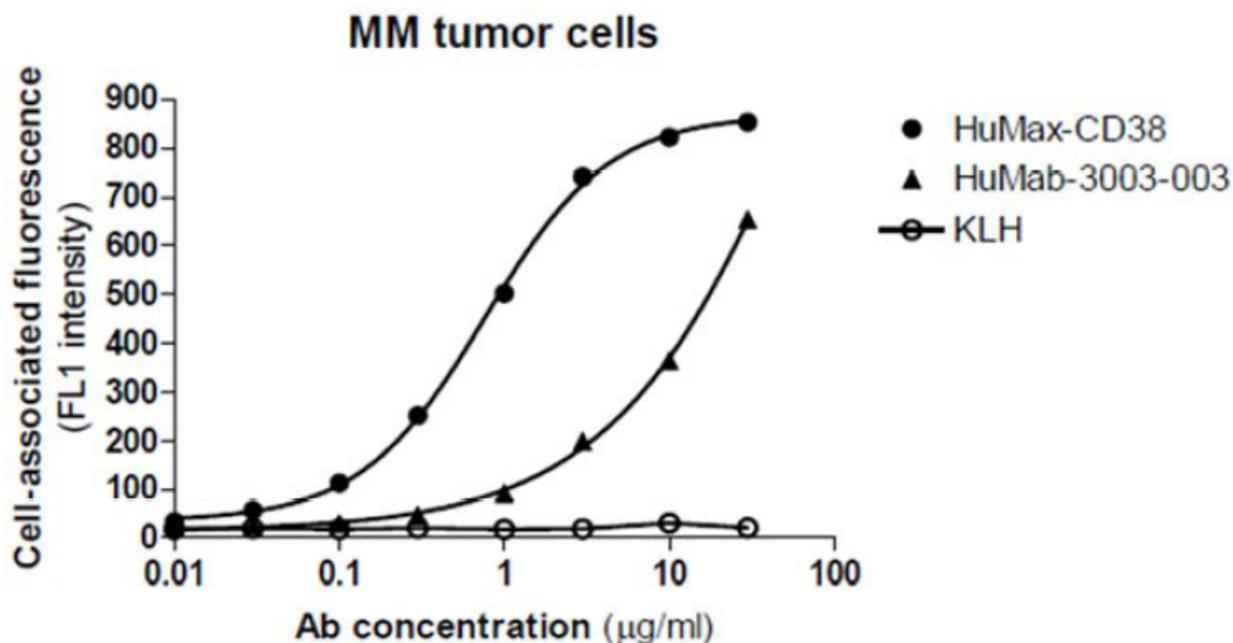


(Excerpted from the submission)

Figure 5. Daratumumab binding to CD38 on CHO-CD38 lymphoma cells in vitro



(Excerpted from the submission)

Figure 6. Daratumumab binding to CD38 on multiple myeloma cells ex vivo

(Excerpted from the submission)

Table 4. EC₅₀ Values for daratumumab and HuMab 3003-003 to CD38 expressing cell lines in vitro

Cell line	Cell type	EC ₅₀ -HuMax-CD38	EC ₅₀ -HuMab-3003-003
Daudi	Lymphoma	0.26 µg/ml	0.99 µg/ml
CHO-CD38	Lymphoma	0.47 µg/ml	0.96 µg/ml
RPMI8226	Multiple myeloma	0.89 µg/ml	4.86 µg/ml

Daratumumab induces complement dependent cytotoxicity (CDC) in malignancies expressing CD38

Study no: GMB3003-003

Methods

Cell lysis was determined using propidium iodide (PI) labelling by flow cytometry. Daratumumab and HuMab-CD38 (HuMab 3003-003) were incubated with both CD38 expressing Daudi lymphoma cells in vitro and freshly isolated multiple myeloma tumor cells from patients ex vivo. CD38 expressing cells were incubated with antibody in the presence of complement-containing human serum. Cell lysis was used as a marker for CDC as determined by uptake of PI.

Results

The mean EC₅₀ for daratumumab was 0.25 µg/mL in Daudi cells with an average lysis of 60%. In multiple myeloma cells isolated ex vivo, the mean maximal lysis was approximately 57% and in 75% of samples lysis was greater than 48%. The surrogate antibody, HuMab-CD38 was inefficient at inducing lysis in many of the cell lines as

indicated by empty data cells shown below (Table 5). Experimental numbers are listed in the first column on the left for each Daudi lymphoma cell culture.

Table 5. Maximal lysis and mean EC₅₀ values of Daudi lymphoma cells

Experiment^a (n)	HuMab-CD38 Max Lysis (EC₅₀)^b	Daratumumab Max Lysis (EC₅₀)^b	Rituximab Max Lysis (EC₅₀)^b
0578-117 DJA (1)	63 (59.09)	64 (0.15)	91 (0.50)
0449-096 DJA (2)	58 (47.95)	71 (0.15)	89 (1.91)
0449-104 DJA (1)		56 (0.44)	81 (3.43)
0449-105 DJA (1)		48 (0.34)	77 (2.80)
0449-106 DJA (1)		62 (0.19)	76 (1.50)
0576-006 KGE (1)	56 (90.84)	56 (0.21)	92 (1.64)
Mean	59 (65.96)	60 (0.25)	84 (1.96)
SD	4 (22.26)	8 (0.12)	7 (1.03)

^a All experiment numbers noted below are reported in report Mod4.2.1.1/GMB 3003-003.

^b Max lysis expressed as %; EC₅₀ values expressed as µg/mL.

EC₅₀ = half maximal effective concentration; daratumumab = referred to in report as P3003-005-1F10; HuMab-CD38 = referred to in report as P3003-003-2F5

(Excerpted from the submission)

Daratumumab induces antibody dependent cell mediated cytotoxicity (ADCC) in malignancies expressing CD38

Study no: GMB3003-004

Methods

Antibody dependent cell mediated cytotoxicity was analysed in vitro as measured by ⁵¹Cr release. Cell lysis was quantified in target cells that were loaded with ⁵¹Cr and incubated with effector cells and antibody.

Results

ADCC was induced by daratumumab in Daudi lymphoma cells with the maximal lysis dependent on the effector cell donor, with average EC₅₀ value for daratumumab of 20.9 ng/mL, HuMab-CD38 of 52.5 ng/mL and rituximab of 55.3 ng/mL. ADCC was also induced in myeloma cell lines JK6L (EC₅₀ 14 ng/mL and 955 ng/mL) and AMO-1 (0.45 µg/mL and 2.9 µg/mL) by daratumumab (P3003-005-1F10) and HuMab-CD38 (P3003-003-2F5) respectively (JK6L cells, Figure 7). ADCC was also tested using the same method on freshly isolated cells from the bone marrow of multiple myeloma patients in four patient samples. Results varied based on the origin of the effector cells. The average maximal lysis was 20.8% for daratumumab for all four patient samples (data not shown).

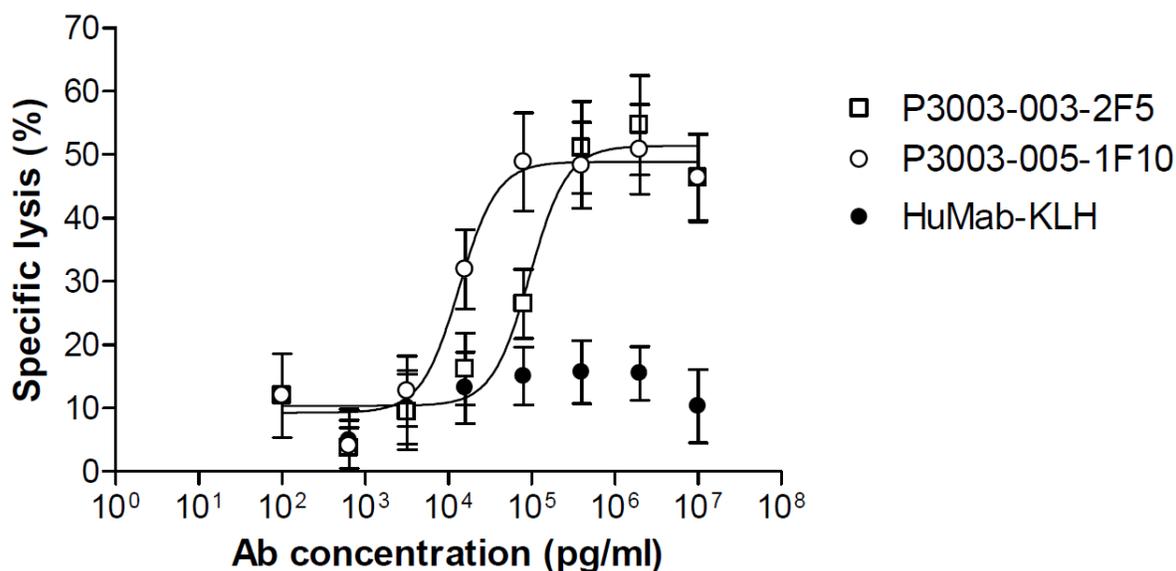
Table 6. Maximal Lysis and EC50 of ADCC by daratumumab and HuMab-CD38 in Daudi lymphoma cells

Exp.No. - Donor	Maximal Lysis (% Specific Lysis)			EC ₅₀ (ng/mL)		
	HuMab-CD38	Daratumumab	Rituximab	HuMab-CD38	Daratumumab	Rituximab
578-118 DJA - A	42	36	55	68	Nc ^a	624
578-118 DJA - B	31	30	25	102	20	57
578-122 DJA - A	76	71	66	41	23	29
578-122 DJA - B	35	28	28	179	147	118
449-091 DJA - A	56	54	43	37	8	38
449-091 DJA - B	70	50	51	80	8	53
Geo Mean	40.2	36.3	36.2	52.5	20.9	55.3
Confidence Interval	30.6-51.5	27.5-46.8	26.9-47.3	35.2-74.4	5.5-51.1	24.8-102.6

^a nc = Non-linear regression did not converge.

EC₅₀ = half maximal effective concentration; Exp. = experiment; No. = number

(Excerpted from the submission)

Figure 7. ADCC of JK6L cells by daratumumab and HuMab-CD38 (P300-003-2F5)

(Excerpted from the submission)

Daratumumab induces antibody dependent cellular phagocytosis (ADCP) in malignancies expressing CD38

Study no: GMB3003-115

Methods

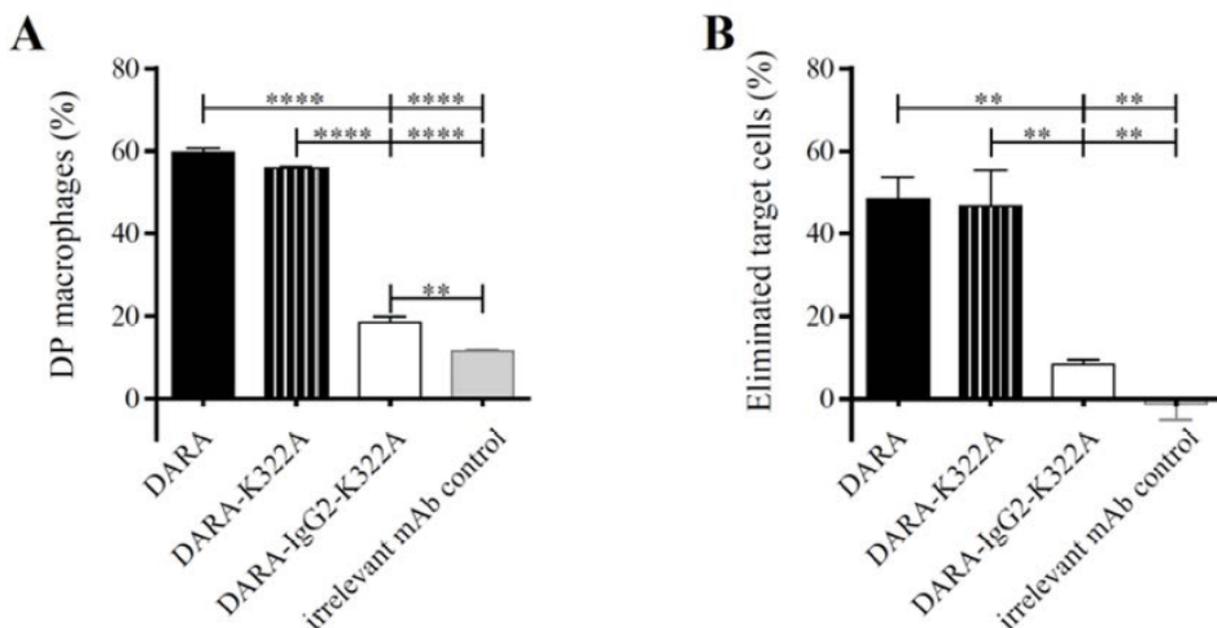
Variant forms of daratumumab antibody were created by altering a residue in the Fc domain (DARA-K322A) to eliminate the complement-activating function or reduce the

phagocytosis stimulating activity through isotype switching to the IgG2 equivalent (DARA-IgG2-K322A). Single dose of isotype matched antibodies or control IgG1 were injected into SCID mice (lacking functional T and natural killer (NK) cells) intraperitoneal at Day 0 or Day 14 at 10 $\mu\text{g}/\text{mouse}$ (0.5 mg/kg; systemic models) or 250 $\mu\text{g}/\text{mouse}$ (12.5 mg/kg; subcutaneous model). Flow cytometry and live cell imaging was used to determine the effect of daratumumab on phagocytosis in mouse and human macrophages using a range of multiple myeloma and Burkitt's lymphoma cell lines and patient derived multiple myeloma cell isolates (including low CD-38 expressing cells).

Results

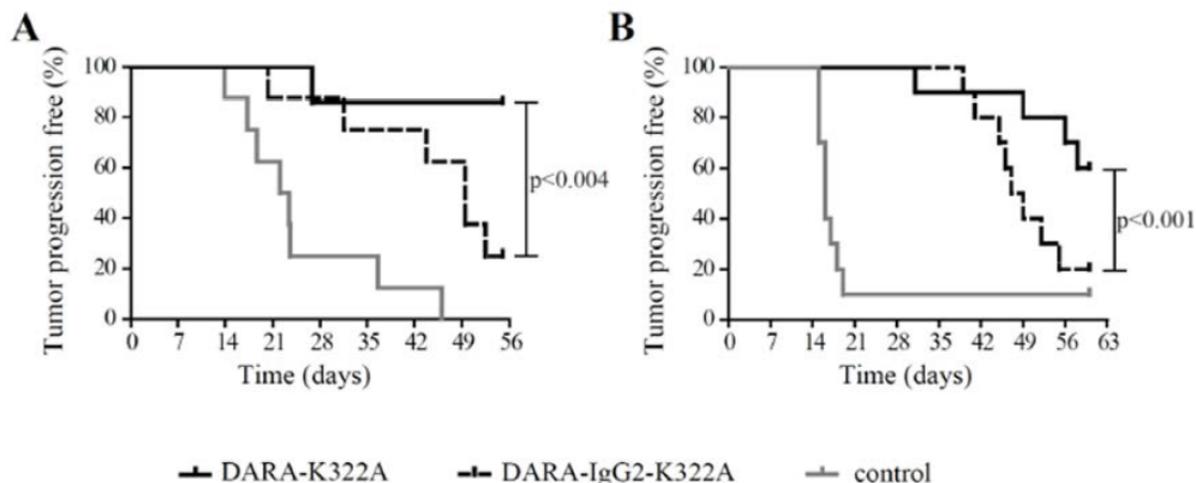
The purpose of these "loss of function" molecules is to examine their effects on mouse macrophages to understand the effect of daratumumab on stimulating tumor cell phagocytosis in vivo. In SCID mice, the DARA-K322A model showed significantly stronger inhibition of tumor growth compared to the DARA-IgG2-K322A model which showed decreased capacity to stimulate phagocytosis or phagocytotic activity (shown as reduced double positive macrophage populations and decreased % of eliminated target cells, Figure 8 A, B below). DARA-K322A in a subcutaneous model using Daudi lymphoma cells impaired tumor growth more than the DARA-IgG2-K322A isoform and additionally provided benefit in a therapeutic model (IV leukemic Daudi-luc xenograft model) in which cells are treated at the time of a tumor challenge (Figure 9A, B). In the figure, DARA-K322A is the dark full line, DARA-IgG2-K322A is the dashed line, and the control is the lightly shaded line. Daratumumab also stimulated phagocytosis in a number of multiple myeloma cell lines, Burkitt's lymphoma cells line, 11 of 12 human myeloma patient samples including low CD-38 expressing patient cells. It is worth noting that one patient with very low CD-38 expression was not susceptible to ADCP by daratumumab.

Figure 8. Daratumumab induction of macrophage mediated phagocytosis in IgG2 isotype variants



(Excerpted from the submission)

Figure 9. Contribution of phagocytosis to in vivo anti-tumor activity by daratumumab



(Excerpted from the submission)

Daratumumab inhibits CD38 enzymatic activity

Study no: GMB3003-013

Methods

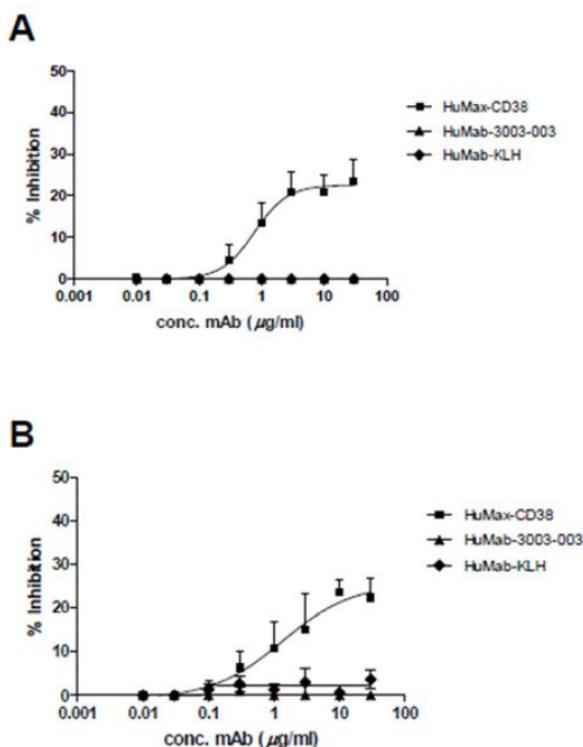
The effect daratumumab or HuMab-CD38 (HuMab -3003-003) on the ADP-ribosyl cyclase activity of CD-38 enzymatic activity was examined by incubation with recombinant CD38 or cellular CD38 in assays using either nicotinamide guanine dinucleotide (NGD) or recombinant CD38 and 8NH₂-NAD as substrates. The isotype specific control, IgG1–Keyhole Limpet Hemocyanin (IgG1 KLH) here abbreviated as “HuMab-KLH” was used as a non-specific isotype control antibody in all experiments. HPLC analysis was used for ribosyl cyclase activity to assess 8-amino-NAD (8NH₂-NAD). Hydrolase activity was examined by quantifying the amount of cADPR hydrolase activity produced from cADPR by HPLC or by measuring the amount of ³²P-ADPR produced from ³²P-cADPR by thin layer chromatography. (Results from both assays were comparable).

Results

In assays using NGD substrate, daratumumab inhibited enzymatic cyclase activity of both forms of CD38 (recombinant and cellular) in a concentration dependent manner. The HuMab-CD38 surrogate antibody did not have an effect on the cyclase activity of either form of CD38 using the NGD substrate (Figure 10). Using 8NH₂-NAD, both daratumumab and HuMab-CD38 inhibited ribosyl cyclase activity (measured as % control of CD38 activity) by 40% and 25% respectively (Figure 11). Daratumumab stimulated the enzymatic activity of cyclic adenosine diphosphate ribose (cADPR) hydrolase of CD38 and HuMab-CD38 inhibited the activity of cADPR. The EC₅₀ for

daratumumab for cADPR was 1.2 $\mu\text{g}/\text{mL}$ and the IC_{50} for HuMab-CD38 for cADPR was 0.2 $\mu\text{g}/\text{mL}$.

Figure 10. Daratumumab inhibits CD-38 enzymatic cyclase activity using NGD substrate

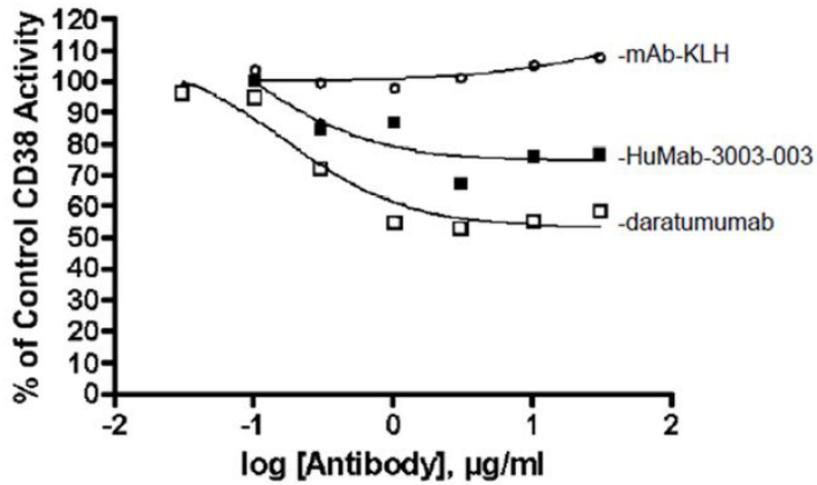


Note: Recombinant His-CD38 (0.6 $\mu\text{g}/\text{mL}$ in 20 mM Tris-HCl supplemented with 30 $\mu\text{g}/\text{mL}$ BSA) or B) CD38-expressing CHO cells were incubated with serial dilutions (0.03, 0.3, 3 and 30 $\mu\text{g}/\text{mL}$ final concentration) of daratumumab or HuMab-CD38. Next, NGD substrate (80 mM) was added, and the conversion of NGD to cGDPR, which when excited at 340 nm emits fluorescence at 430 nm, was measured using an Envision fluorescence microplate reader. Mean \pm SEM (3 experiments performed in duplicate).

Key: BSA = bovine serum albumin; cGDPR = cyclic guanosine diphosphate ribose; CHO = Chinese Hamster Ovary; daratumumab = HuMax-CD38; HuMab-CD38 = HuMab-3003-003; HuMab-KLH = human anti-keyhole limpet hemocyanin; mAb = monoclonal antibody; NGD = nicotinamide guanine dinucleotide; SEM = standard error of the mean

(Excerpted from the submission)

Figure 11. Daratumumab inhibits enzymatic ribosyl cylcase activity of CD38 using 8-amino-NAD substrate

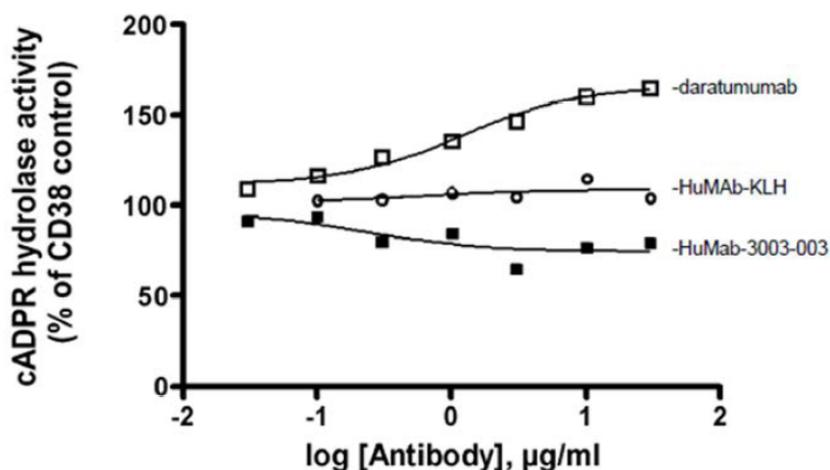


Note: Dilutions of antibodies and recombinant CD38 protein were mixed, and the cyclase reaction was initiated by mixing the CD38/antibody mixture with 8NH₂-NAD. The reaction was stopped by filtration, and reaction products were analyzed by reverse-phase HPLC.

Key: HPLC = high pressure liquid chromatography; HuMab-CD38 = HuMab-3003-003; mAb-KLH = human anti-keyhole limpet hemocyanin; mAb = monoclonal antibody

(Excerpted from the submission)

Figure 12. Daratumumab promotes enzymatic cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of CD38



Note: The cADPR hydrolase reaction was initiated by adding 20 µL of CD38/antibody mixture to 5 µL of a mixture containing 0.5 mM cADPR and approximately 0.1 µCi of ^{32}P -cADPR. After incubation, the reaction product was analyzed by PEI-cellulose thin layer chromatography and quantitated using a Packard Cyclone Phosphorimager (Meriden, CT) to determine the amount of ^{32}P -ADPR or ^{32}P -NAD produced.

Key: cADPR = cyclic adenosine diphosphate ribose; HuMab-CD38 = HuMab-3003-003; HuMab-KLH = human anti-keyhole limpet hemocyanin

(Excerpted from the submission)

Daratumumab induces B-cell apoptosis

Study no: GMB3003-011

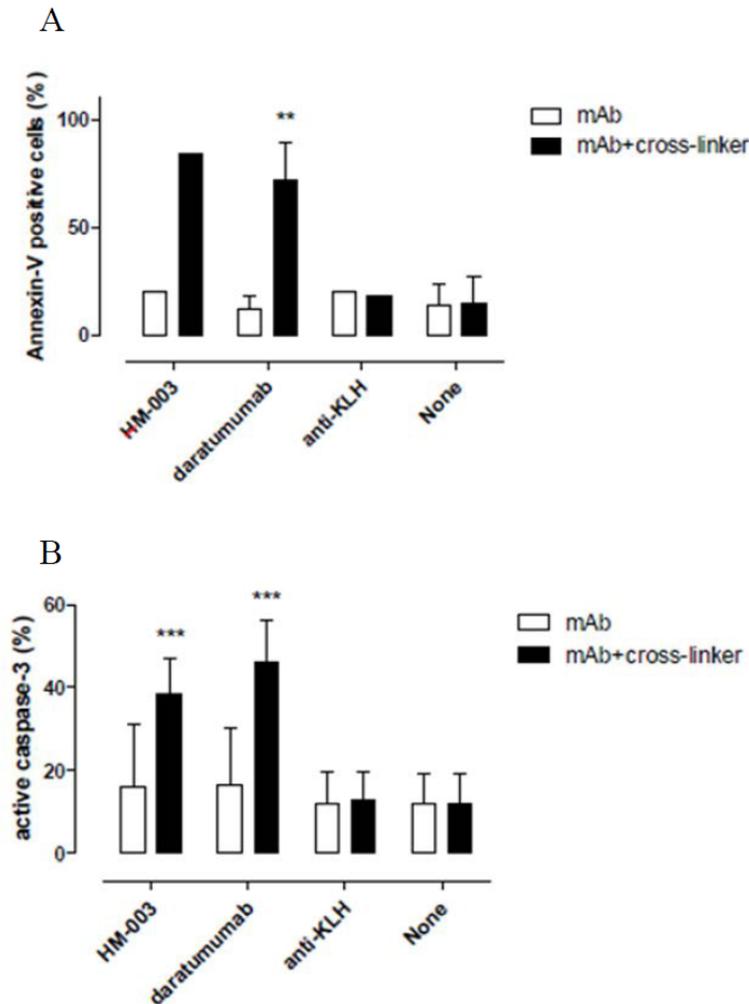
Methods

Ramos or luciferase-transfected Daudi lymphoma cell lines were cultured with daratumumab (1 µg/mL), HuMab-CD38 antibody denoted here as HM-003 (10 µg/mL), or isotype control antibody HuMab-KLH (10 µg/mL), in the presence or absence of cross-linking anti-huIgG (10 µg/mL) for 24 hours and apoptosis was measured by staining with annexin-V and PI, or active caspase-3.

Results

Daratumumab and HuMab-38 induced apoptosis in the presence of cross linking antibody only, as measured by annexinV/PI and caspase-3 staining in Ramos, OPM-1 and Daudi cell lines (Figure 13, Table 7). Measures of apoptosis were not significantly induced without cross linking agent (daratumumab or HuMab-CD38 alone).

Figure 13. Induction of apoptosis by daratumumab after secondary antibody cross-linking in Ramos lymphoma cell lines



Note: Ramos cells were cultured in the presence of 1 $\mu\text{g}/\text{mL}$ CD38 or isotype control (anti-KLH) antibodies, with or without cross-linking antibody (10 $\mu\text{g}/\text{mL}$). A) Staining with annexin V-FITC and PI; data represent mean values of positive cells for HuMab-CD38, anti-KLH (n=2), and mean \pm SD values for daratumumab and culture medium (n=5). B) Measurement of active caspase-3. Data represent mean \pm SD (n=3) of percent positive cells. **P = 0.002, daratumumab vs. none (Student's *t*-test); ***P < 0.0001, HuMab-CD38 and daratumumab vs. anti-KLH or medium, after mAb cross-linking (Repeated Measures ANOVA, post hoc Tukey test).

Key: FITC = fluorescein isothiocyanate; HM-003 = HuMab-CD38; KLH = Keyhole Limpet Hemocyanin; mAb = monoclonal antibody; n = number; PI = propidium iodide; SD = standard deviation

(Excerpted from the submission)

Table 7. Summary of apoptosis induced by daratumumab in CD38-positive expressing cell lines after crosslinking

Experiment	<u>Annexin V/PI^a</u>			<u>Caspase-3^a</u>		
	Ramos	OPM-1	Daudi-luc	Ramos	OPM-1	Daudi-luc
3003-2050-350	39.6	13.8	17.3	24.1	7.8	7.5
3003-2050-352	40.6	10.5	24.0	46.5	23.1	22.1
3003-2050-365	49.6	19.9	23.8	39.6	21.4	19.3
Mean (SD)	43.3 (5.50)	14.7 (4.8)	21.7 (3.8)	36.7 (11.5)	17.4 (8.4)	16.3 (7.7)

^a Data represented as (% apoptosis treated) – (% apoptosis background).

SD = standard deviation

(Excerpted from the submission)

Daratumumab induces apoptosis via Fc gamma receptor mediated crosslinking

Study no: GMB3003-116

Methods

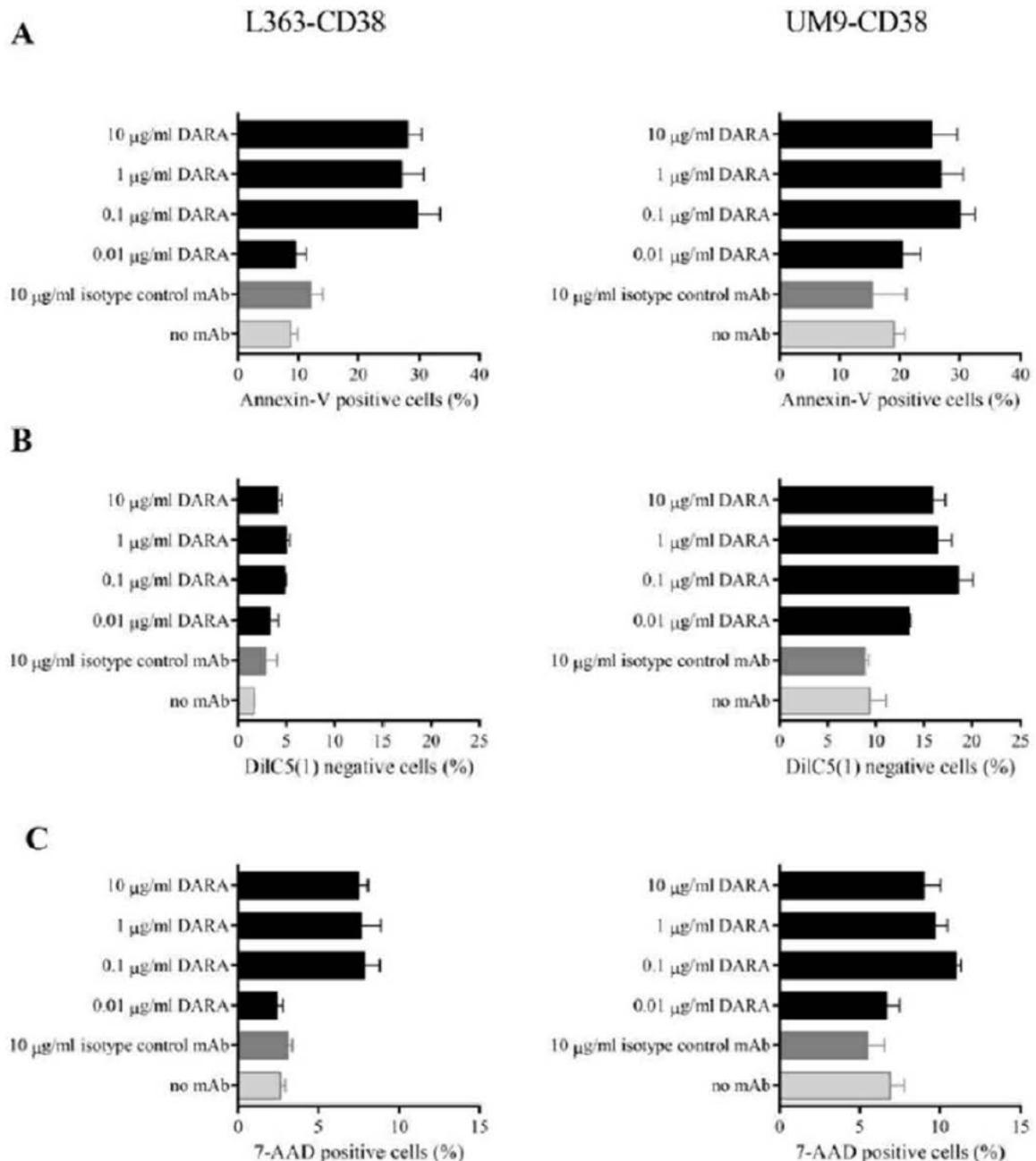
Myeloma cell lines (CD38 transduced L363 and UM9) were incubated with daratumumab (DARA) or isotype control antibody and Fc-crosslinking secondary antibody for 24 hours. Apoptosis was measured by positive staining of 7-aminoactinomycin (7-ADD), Annexin-V and loss of mitochondrial membrane potential (DiIC5 (1) negative cells). Depolarization was measured with the MitoProbe 1,1',3,3',3',3'-hexamethylindodicarbo - cyanine iodide (DiIC5(1)) kit, (Life Technologies) and quantified as % DiIC5 negative cells. In vivo interactions were examined in both FcR γ -chain knockout mice (FcR γ ^{-/-}) and NOTAM mice which have normal surface expression of Fc γ R but are deficient in their ability to signal due to a loss of Fc γ R function (introduction of mutations in transgenic model). Cell types with the potential to illicit Fc crosslinking include in general, leukocytes, but more specifically expected are natural killer cells, monocytes, macrophages or endothelial cells. Leukocytes can illicit Fc γ R-mediated antibody crosslinking in NOTAM mice without causing cell death by ADCC or phagocytosis. In Fc γ R^{-/-} mice leukocytes only express the inhibitory Fc γ RIIb, and lack of the activating Fc γ R (Fc γ RI, Fc γ RIII and Fc γ RIV). CD38 expressing EL4 were labeled with carboxyfluorescein succinimidyl ester (CFSE) and intraperitoneally injected into both NOTAM and Fc γ R^{-/-} mice. Mice were treated with 2 μ g DARA-K322A (0.1 mg/kg), following 4 hour incubation, cells were harvested by peritoneal lavage and analysed by flow cytometry for markers of apoptosis (7-ADD and Annexin-V).

Results

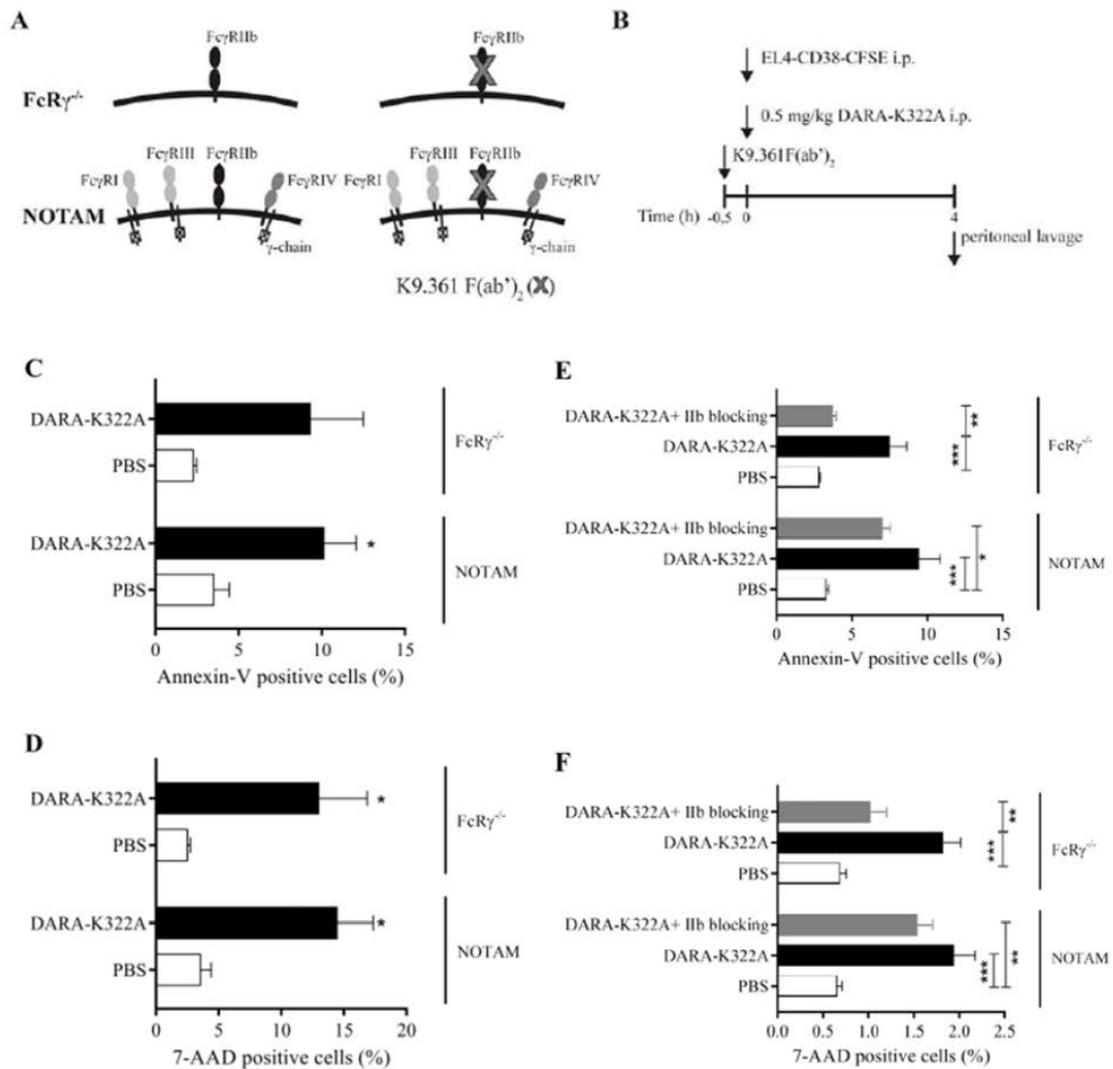
In vitro, daratumumab promoted apoptosis in the presence of Fc cross linking antibody as measured by 7-ADD, increased Annexin-V staining and loss of mitochondrial membrane potential (Figure 14). In vivo, DARA-K322A (variant form of daratumumab with mutant residue in the Fc domain) promoted increased number of apoptotic cells in both the Fc γ R^{-/-} mice and the NOTAM mice as measured by 7-ADD and Annexin-V staining (Figure 14). When Fc γ RIIB was blocked prior to treatment (Figure 15 E, F), cell death returned to baseline in Fc γ R^{-/-} mice, however there was still a large population of

apoptotic cells measured by both 7-ADD and Annexin-V staining in NOTAM mice, indicating the involvement of other Fc receptors in mediating crosslinking to result in cell death (Fc γ RI, Fc γ RIII and Fc γ RIV).

Figure 14. Daratumumab induces apoptosis via Fc mediated crosslinking in vitro



(Excerpted from the submission)

Figure 15. Daratumumab induces apoptosis via Fc mediated crosslinking in vivo

Note: A) Schematic representation of the available FcγRs in the different mouse models. B) Scheme of the syngeneic peritoneal mouse model. NOTAM and FcγR^{-/-} mice were treated with FcγRIIb blocking F(ab')₂ fragments (K9.361 F(ab')₂) 30 min. prior to tumor cell inoculation. Subsequently, 5 × 10⁶ CFSE labeled EL4-CD38 cells were inoculated IP, followed by DARA-K322A (2 μg/mouse) or PBS treatment. After 4 h tumor cells in the peritoneal wash were analyzed by flow cytometry. C, E) percentage Annexin-V positive cells. D, F) percentage 7-AAD positive cells. (4-6 mice/group (Mean ± SD); * P < 0.05, ** P < 0.01, *** P < 0.001 unpaired *t*-test (C, E) or Bonferroni's multiple comparison test [D, F]).

Key: CFSE = carboxyfluorescein succinimidyl ester; DARA-K322A = mutant form of daratumumab, which lacks CDC activity; h = hour; IP = intraperitoneally; min. = minute; PBS = phosphate buffered saline

(Excerpted from the submission)

Daratumumab reduces tumor burden in human CD38 expressing lymphoma xenograft mouse model

Study nos: GMB3003-017

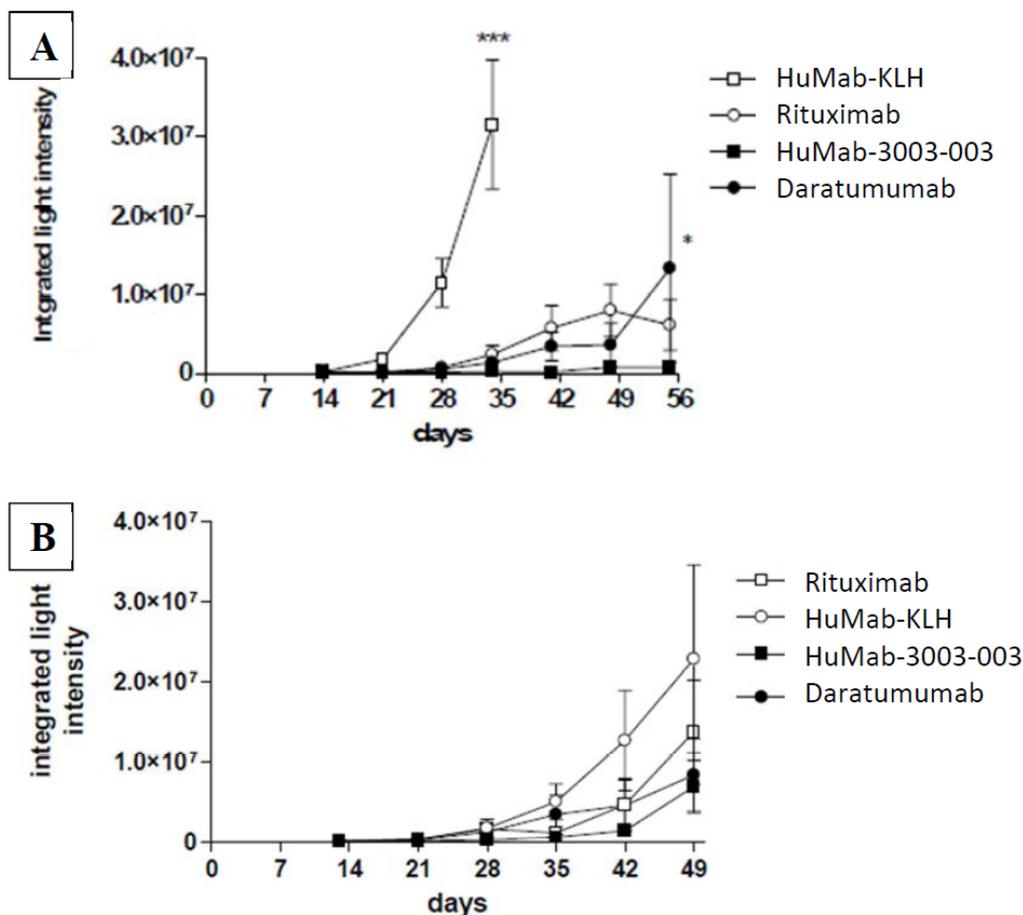
Methods

SCID mice were injected with luciferase expressing Daudi human lymphoma cells intravenously (Burkitt's lymphoma origin) followed injection with daratumumab (LC3003-335), HuMab-CD38 (HuMab-3003-003, P3003-0032F5), rituximab or antibody isotype control HuMab-KLH. The treatment consisted of 100 µg/mouse on Day 1, 300 µg/mouse on Day 7 or 10 µg/mouse on Day 14. Optical imaging was used to assess tumor growth or burden by the production of light following administration of luciferin which is reactive with luciferase expressing lymphoma cells (bioluminescence).

Results

Daratumumab administered at Day 7 reduced tumor growth compared to isotype control when measured on Days 28, 34 and 55 (Figure 16A). On Day 55, daratumumab treatment was not significantly different from HuMab-CD38 or rituximab control groups in regards to tumor burden. Daratumumab or HuMab-CD38 administered at Day 14 significantly reduced tumor growth and burden as compared to isotype control (Figure 16B). Bioluminescence images from mice treated with daratumumab on Day 14 shows that daratumumab, rituximab, and HuMab-CD38 delayed tumor growth as measured on Day 49 compared to HuMab-KLH control (Figure 17).

Figure 16. Daratumumab reduces tumor growth in human lymphoma xenograft SCID mouse model

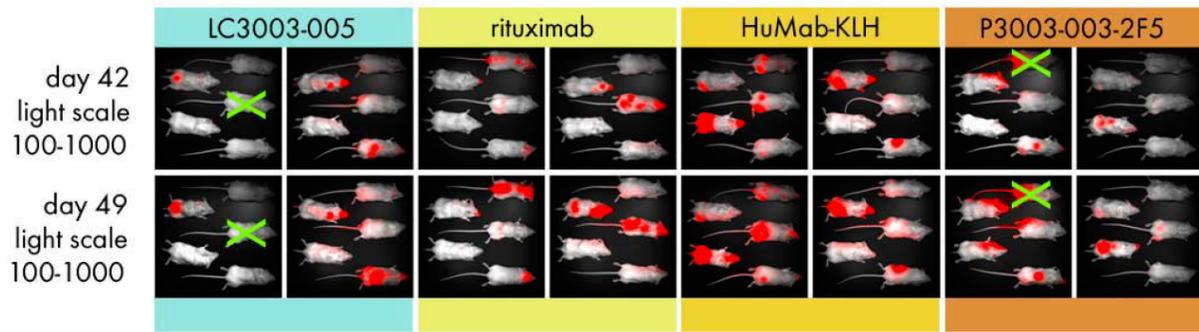


Note: SCID mice were inoculated IV with Daudi-luc cells (2.5×10^6). The integrated light intensity representing tumor load was measured, and data are presented as mean \pm SEM. A) Antibodies were injected IP seven days after tumor cell inoculation ($300 \mu\text{g}/\text{mouse}$, $n = 4$ or 5 mice per group). *** $P < 0.001$, HuMab-KLH vs. other treatments on Day 28 and Day 35 (one-way ANOVA); * $P < 0.01$, HuMab-CD38 vs. daratumumab (two-way ANOVA). B) Antibodies were injected IP 14 days after tumor cell inoculation ($10 \mu\text{g}/\text{mouse}$, $n = 6$). At Day 49, tumor growth was reduced by daratumumab and HuMab-CD38 vs. control ($P < 0.05$; two-way ANOVA).

Key: HuMab-CD38 = HuMab-3003-003; IP = intraperitoneal; IV = intravenous; HuMab-KLH = human anti-keyhole limpet hemocyanin; n = number; SCID = severe combined immunodeficiency; SEM = standard error of the mean

(Excerpted from the submission)

Figure 17. Bioluminescence images of individual mice treated with daratumumab from human lymphoma xenograft SCID mouse model



(Excerpted from the submission)

**Daratumumab mediates proliferation and cytokine release in human blood cells
ex vivo**

Study no: GMB3003-018

Methods

To explore the potential for daratumumab to induced cytokine release and proliferation, human isolated PBMCs and human whole blood samples (8 donors) were used with five methods of incubation to exposure of daratumumab including: Antibody in solution, wet coating, dry coating (air-dried), Fc-capture (anti-Fc plus wet-coated antibody), or aqueous antibody applied to an endothelial cell monolayer. Secondary endpoints were measured by ELISA. Daratumumab was compared against a non-specific isotype control, IgG1-KLH. Positive controls for cytokine release included lipopolysaccharide (LPS), anti-CD3 antibody, CAMPATH-1 and anti-CD52. Proliferation was measured using ^3H –thymidine incorporation.

Results

All positive controls induced a strong cytokine release and a significant effect on proliferation. Daratumumab induced release of IL-1 β , IL-6 and IFN- γ compared to the isotype specific control IgG1–KLH at the highest concentration tested (100 $\mu\text{g}/\text{ml}$). Fc mediated effects were examined (using a culture medium alone control), employing the soluble or wet coated antibody method. TNF- α and granzyme A were observed in culture media 24 hours following treatment in 4 of 8 donors. Using dry coating, IL-6 and TNF- α were observed in culture media 24 and 72 hours following treatment and IL-1 β , IL-6 and TNF- α were observed in the remaining donor blood samples. The cytokine response in these donor blood samples was paralleled with a high response to the antibody isotype control which is expected with an Fc-related effect. See Table 8 for a summary of the therapeutic agents that elicit a cytokine response compared to medium alone, now including daratumumab.

Table 8. Therapeutic agents stimulating cytokine release compared to medium alone

	$\mu\text{g/mL}$	Soluble		Dry-Coat		Anti-Fc	
		MNC	WB	MNC	WB	MNC	WB
IL-1β	1						
	100		KLH	KLH/IVIG		KLH	
IL-6	1			Daratumumab Rituximab Cetuximab KLH	KLH	Daratumumab	Daratumumab Bevacizumab KLH/IVIG
	100	KLH	KLH	Daratumumab all other Abs (exc. Natalizumab) KLH	Daratumumab all other Abs (exc. Natalizumab and Bevacizumab) KLH	Daratumumab Basiliximab KLH	Daratumumab Bevacizumab KLH/IVIG
TNF-α	1			Daratumumab all other abs (exc. Natalizumab and Daclizumab)			
	100	KLH	KLH	Daratumumab all other Abs		KLH	

Abs = antibodies; IVIG = intravenous immunoglobulin; KLH = Anti-Keyhole Limpet Hemocyanin;
MNCs = mononuclear cells; WB = whole blood

(Excerpted from the submission)

Binding of HuMax-CD38 to chimpanzee and human platelets at 4°C and at room temperature

Study no: BKV00015

Methods

Chimpanzee and human blood samples (n=3, each) were collected and direct labeling was assessed at room temperature and 4°C using a concentration range of HuMax-CD38-FITC (100, 33, 11, 3.70, 1.23, 0.41, 0.14, and 0.05 $\mu\text{g/mL}$). Samples were counterstained with anti-CD61 to distinguish platelets among whole blood. Samples were analyzed by flow cytometry.

Results

There was no clear difference in labeling based in incubation temperature. In chimpanzee blood samples incubated at 4°C, positive binding was observed in approximately 60% of gated platelets between 3.7 and 100 $\mu\text{g/mL}$ HuMax-CD38-FITC, decreasing to approximately 3% at the 0.05 $\mu\text{g/mL}$ antibody concentration. At room temperature binding was observed at 70% of gated platelets between 1.23 and 100 $\mu\text{g/mL}$, decreasing to 8% at 0.05 $\mu\text{g/mL}$ HuMax-CD38-FITC.

In human blood samples incubated at 4°C, 45% of gated platelets at 100 µg/mL HuMax-CD38-FITC exhibited binding, with a decrease to 14% at 1.23 µg/mL HuMax-CD38 FITC. In human blood samples incubated at room temperature, HuMax-CD38-FITC binding to gated platelets was 43% at 100 µg/mL and decreased to 28% at 3.7 µg/mL HuMax-CD38-FITC.

Binding of HuMab-3003-003 (HuMAB-CD38) and HuMax-CD38 to cynomolgus monkey and human blood cells

Study no: SR3003-06-31

Methods

Peripheral blood was collected from humans and cynomolgus monkeys, incubated with HuMab-CD38, daratumumab or anti-KLH isotype control Ab in vitro. B and T lymphocytes were identified by co-staining with antibodies against CD20 and CD3, respectively and using PE, PerCP or FITC to analyze staining by flow cytometry and to determine binding. Erythrocytes and granulocytes were identified based on light scatter properties in the flow cytometer.

Results

Daratumumab and HuMab-CD38 (100 µg/ml) did not bind strongly to human B and T cells (n=2), exhibited by mean fluorescence intensity values (MFI) of 30-250 units. In cynomolgus monkey B and T cells, HuMab-CD38 bound strongly, with MFI values of 1000-3000 at the same concentration (n=3) while daratumumab did not exhibit specific binding to cynomolgus monkey B or T cells under these conditions. Neither daratumumab or HuMab-CD38 bound to human or cynomolgus monkey granulocytes at greater levels than those observed with the nonspecific isotype control. Daratumumab did not bind to human or cynomolgus monkey erythrocytes, nor did the nonspecific isotype control. HuMab-CD38 did bind to cynomolgus monkey erythrocytes at concentrations greater than or equal to 3 µg/mL with a maximal MFI of 175 units, but binding to human erythrocytes was not observed.

Antibody induced complement mediated lysis of human erythrocytes

Study no: SR3003-06-67

Methods

Human erythrocytes were incubated with daratumumab or HuMab-CD38 (10 µg/mL or 100 µg/mL) in the presence of human AB serum as a source of complement (negative control, heat inactivated serum). Anti-KLH antibody was used as an isotype control antibody and human serum containing antibodies directed against the blood group P antigen was used as a positive control antibody source. Optical absorbance at 405 nm was used to measure cellular lysis.

Results

Daratumumab and HuMab-CD38 did not cause any complement mediated lysis of erythrocytes, and was comparable to the negative control anti-KLH. Induction of lysis by the positive control was effective in all samples tested.

4.2 Secondary Pharmacology

Studies not reviewed.

4.3 Safety Pharmacology

Stand-alone safety pharmacology studies were not conducted.

5 Pharmacokinetics/ADME/Toxicokinetics**5.1 PK/ADME**

Studies not reviewed.

6 General Toxicology**6.1 Single-Dose Toxicity**

Studies not conducted.

6.2 Repeat-Dose Toxicity

Study title: Multiple Dose Safety Study in Chimpanzees with a 2-month Recovery Period

The following study was initially reviewed under IND100638 by Stacey Ricci PhD and parts of it were reformatted to fit this NDA review.

Study no.:	8754-0701
Study report location:	eCTD 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	16 March 2007
GLP compliance:	Signed and included
QA statement:	Signed and included
Drug, lot #, and % purity:	Daratumumab, lot # P273934, 99.2% purity (IgG SDS-PAGE) (b) (4)

Key Study Findings

- There was one mortality at 5 mg/kg immediately following dosing (1.5 hours) in a female chimpanzee due to cytokine release response with overinflation, edema of the lungs following dosing with detectable levels of cytokines TNF- α , IL-6 and IFN- γ in the serum prior to necropsy.
- Clinical signs include dyspnea, sneezing, increased mucous production, evacuation of bowels, mucous membrane pallor, diarrhea, soft stool, reduced appetite, respiratory arrest, and subsequent cardiac arrest.
- Toxicologically significant daratumumab hematology findings included severe thrombocytopenia, anemia, and leukopenia during study period. Most adverse effects on hematology were recovering by the end of the two-month recovery period.
- Toxicologically significant daratumumab related changes in clinical chemistry parameters included elevated AST, ALT, LDH, decreased levels of IgM and IgG, and elevated CRP. Elevated liver parameters and LDH returned to normal during the first recovery time point (4 weeks recovery); recovery in CRP was observed by the end of the observation period and was persistent through recovery; IgG and IgM levels did not recover to pretrial levels.

Methods

Doses: 0, 5, 25 mg/kg
 Frequency of dosing: Once weekly (6 total doses)- conditioning dose, of 10 mg was administered 24 hours prior to first infusion of high dose following cytokine response reaction in first dosing of two low dose animals
 Route of administration: Intravenous infusion
 Dose volume: Based on the most recent body weight measurement collected on the morning of dosing
 Formulation/Vehicle: (b) (4) Sodium Acetate / (b) (4) Sodium Chloride / 1 (b) (4) Mannitol / (b) (4) % Polysorbate 20 pH 5.5. Animals received an intravenous dose of vehicle 1 week prior to dosing of drug.
 Species/Strain: Chimpanzees
 Number/Sex/Group: 2 male, 3 female; 1/sex/group
 Age: 10-15 years old
 Weight: 42.24-55.91 kg
 Satellite groups: N/A
 Unique study design: N/A
 Deviation from study protocol: None impacted study results or objectives

Table 9. Baseline characteristics for repeat dose toxicity study in chimpanzees

ID#	Sex	Date of Birth	Body Weight
96A009	M	28 Apr 96	53.17 kg
92A016	F	23 Dec 92	55.91 kg
95A015	F	07 Oct 95	49.00 kg
96A015	M	28 Jul 96	54.95 kg
96A017	F	12 Aug 96	42.24 kg

*(Excerpted from the submission)***Table 10. Study design for repeat dose toxicity study in chimpanzees**

Group	ID#	Sex	Dose level (mg/kg)	Dose Route	Number of Doses
1	96A009	M	5	i.v.	6
	92A016	F			1
N/A	95A015	F	5	i.v.	2
2	96A015	M	25	i.v.	6
	96A017	F			

(Excerpted from the submission)

Observations and Results

Mortality

One group 1 (5 mg/kg) female chimpanzee (#92A016) died 1.5 hours after the first dose of daratumumab due to apparent cytokine release response. Measureable levels of TNF- α , IL-6 and IFN- γ were detected in the serum prior to terminal necropsy (pretrial levels were below the limit of quantitation). The following is excerpted from IND100638 review:

The pathologist concluded that this animal's death was attributed to fluid accumulation in the lung considered likely the result of test article-induced acute anaphylaxis. "Over inflation and edema of the lung were considered the likely cause of death for chimpanzee 92A016. These findings in conjunction with clinical observations of dyspnea, pallor of the mucus membranes, respiratory arrest and cardiac arrest immediately following the administration of HuMax-CD38 strongly suggest anaphylaxis as the cause of the pulmonary fluid accumulation (p. 479 NIRC 8754-0701, Pathology Report.)"

Clinical Signs

In addition to the death of the female chimpanzee in the 5 mg/kg dose group, two additional group 1 animals (at 5 mg/kg) exhibited a cytokine release response, including increased tracheal and nasal mucous production. Animal 96A009 evacuated the lower bowel approximately 10 minutes following the first dose and again at 30 minutes post first dose.

Both Group 2 animals showed a reaction to the initial 25 mg/kg dose. Clinical signs included sneezing and mucous production was noted in A96A017 approximately 15 minutes (25mL) into the dosing; this activity subsided and mucous membrane pallor was noted following administration of 44 mL of the dose (26 minutes). Animal 96A015 exhibited increased mucous production and sneezing following administration of approximately 20 mL of the first 25 mg/kg dose (12 minutes). This sneezing subsided at 50 mL of infusion and increased mucous was present in the trachea 30 minutes post-dose. The animal evacuated its bowel 37 minutes post-dose. Sporadic episodes of soft stool with good stool were observed with virtually all animals. The Group 2 animals experienced more severe gastrointestinal problems during the recovery period. Animal 96A015 had a prolonged bout of diarrhea beginning on Day 86 and extending through Day 106 and blood was observed in the stool on Day 105. Reduced appetite and hypoactivity/depression were also reported for this animal (#96A015). Animal 96A017 had diarrhea and a reduced appetite on Days 103-105 and had multiple reports of diarrhea, soft stool and reduced appetite through the end of the study. Both animals received antimicrobials and supportive therapy, but were slow to respond to treatment (96A015, 96A017). Animals 96A009, 95A015 and 96A017 repeatedly self-mutilated and opened biopsy sites following biopsy procedures.

Body Weights

Body weights were unremarkable with the exception of one animal (96A015) which showed a significant decrease in body weight during the recovery period correlating with an adverse clinical episode.

Feed Consumption

Unremarkable

Ophthalmoscopy

Unremarkable

ECG

Unremarkable; additional cardiovascular and respiratory parameters examined included respiratory rate, body temperature and pulse rate.

Hematology

Table 11. Hematology findings from repeat dose toxicity study in chimpanzees

Hematology parameter	% change from pretrial levels				
	males		females		
sex	5	25	5	5	25
daratumumab (mg/kg)					
animal #	96A009	96A015	92A016	95A015	96A017
Hemoglobin (g/dL)					
Main study- post dose 6	-21	-37	n/a	n/a	-22
Recovery- Day 71	-24	n/a	n/a	-4	n/a
Recovery- Day 147	-4	-28	n/a	n/a	-16
Hematocrit (%)					
Main study- post dose 6	-19	-36	n/a	n/a	-23
Recovery- Day 71	-25	n/a	n/a	-2	n/a
Recovery- Day 147	-4	-26	n/a	n/a	-14
RBC ($10^6/\text{mm}^3$)					
Main study- post dose 6	-19	-37	n/a	n/a	-25
Recovery- Day 71	-28	n/a	n/a	-9	n/a
Recovery- Day 147	174	112	n/a	n/a	123
White cell count ($10^3/\text{mm}^3$)					
Main study- post dose 6	6	90	n/a	n/a	69
Recovery- Day 71	-32	n/a	n/a	-34	n/a
Recovery- Day 147	-37	-5	n/a	n/a	-61
Platelets ($10^3/\text{mm}^3$)					
Main study- post dose 6	-70	-93	n/a	n/a	-73
Recovery- Day 71	-44	n/a	n/a	23	n/a
Recovery- Day 147	-5	-28	n/a	n/a	-35

RBC: Red blood cells, n/a: data not available for given time point

Clinical Chemistry

Table 12. Clinical chemistry findings from repeat dose toxicity study in chimpanzees

Clinical chemistry parameter	% change from pretrial				
	Males		Females		
Sex					
Daratumumab (mg/kg)	5	25	5	5	25
Animal #	96A009	96A015	92A016	95A015	96A017
AST (U/L)					
Pretrial					
Main study- post dose 6	1382	1891	n/a	n/a	1126
Recovery- Day 71	-23	n/a	n/a	-64	n/a
Recovery- Day147	-14	-22	n/a	n/a	0
ALT (U/L)					
Pretrial					
Main study- post dose 6	147	375	n/a	n/a	108
Recovery- Day 71	-4	n/a	n/a	-4	n/a
Recovery- Day147	-13	-18	n/a	n/a	0
LDH (U/L)					
Pretrial					
Main study- post dose 6	200	187	n/a	n/a	192
Recovery- Day 71	-13	n/a	n/a	-29	n/a
Recovery- Day 147	-16	3	n/a	n/a	-2
IgM (mg/dL)					
Pretrial					
Main study- post dose 6	-78	-87	n/a	n/a	-87
Recovery- Day 71	-78	n/a	n/a	-100	n/a
Recovery- Day 147	-67	-77	n/a	n/a	-79
IgG (mg/dL)					
Pretrial					
Main study- post dose 6	-60	-46	n/a	n/a	-39
Recovery- Day 71	-62	n/a	n/a	-41	n/a
Recovery- Day 147	-10	-53	n/a	n/a	-44
CRP (mg/dL)					
Pretrial					
Main study- post dose 6	850	6750	n/a	n/a	3650
Recovery- Day 71	0	n/a	n/a	0	n/a
Recovery- Day 147	0	300	n/a	n/a	0

AST: aspartate transaminase, ALT:alanine transaminase, LDH:lactate dehydrogenase, CRP: c-reactive protein,n/a: data not available for given time point

Urinalysis

Unremarkable

Gross Pathology

Gross necropsy – Not performed on study animals; only unscheduled death necropsy performed. Notable gross necropsy findings for chimpanzee 92A016 consisted of overinflation and edema of the lungs, foci of lung anthracosis, thickening of the left ventricle, the presence of a large (chronic) infarct on the surface of the right ventricle and multiple adhesions of the stomach and intestinal loops.

Organ Weights

Not performed on study animals.

Histopathology

Adequate Battery: Yes, lymph node and skin biopsies were performed

Peer Review: No

Histological Findings:

No alterations in skin were attributable to drug.

Excerpted from IND100638: Decreases in the size and/or number of lymphoid follicles within the node were observed at one or more time points in chimpanzees # 96A009 (low-dose; Days 43 and 71) and # 96A017 (high dose; Days 37 and 57) and in # 92A016 (pretrial). Because of the pretrial observation, the decreases were not considered drug related by Genmab.

Special Evaluation-Direct Antiglobulin Test

Unremarkable

Toxicokinetics

- Appeared non-linear between 5 mg/kg and 25 mg/kg due to increases in $t_{1/2}$, with increasing dose and number of administrations.
- $T_{1/2}$ ranged from 15.5-18.8 days.
- Daratumumab concentrations returned to near pre-trial levels approximately one month following the final dose in the 5 mg/kg dose group, and approximately two months following the final dose in the 25 mg/kg dose group

Table 13. Summary of toxicokinetics from repeat dose toxicity study in chimpanzees

Dose (mg/kg)	Day	Dosing Day ^{c)}	Animal No.	C _{max} (µg/ml)	t _{max} (h)	AUC(0-t) ^{d)} (h·µg/ml)	AUC (h·µg/ml)	AUC _{corr} ^{a)} (h·µg/ml)	AUC% _{Extrap} (%)	t _{1/2} (h)	V _d (ml/kg)	CL (ml/h/kg)
5	7	0	95A015	86	0.58	2799	2966	-	5.6	36	86.7	1.69
	7	0	96A009	100	0.58	2185	2246	-	2.7	38	122.7	2.23
21	14	0	96A009	129	24.00	11309	15836	14506	28.6	88	43.8 ^{b)}	0.34 ^{b)}
	42	35	96A009	129	2.00	21450	23171	14929	7.4	132	63.8 ^{b)}	0.33 ^{b)}
25	22	0	96A015	612	0.58	25885	40463	-	36.0	103	91.4	0.62
	22	0	96A017	778	0.58	39158	74458	-	47.4	135	65.6	0.34
35	14	0	96A015	630	0.58	39995	96676	34711	58.6	231	240.0 ^{b)}	0.72 ^{b)}
	35	14	96A017	599	0.58	62112	215145	73347	71.1	335	164.7 ^{b)}	0.34 ^{b)}
56	35	0	96A015	695	0.58	146729	319583	9747	54.1	596	2205.3 ^{b)}	2.56 ^{b)}
	56	35	96A017	967	0.58	201462	364102	43254	44.7	461	384.4 ^{b)}	0.58 ^{b)}

^{a)} AUC corrected by subtracting rest area from previous dosing ($AUC_{corr} = AUC - C(0)/\lambda_2$)

^{b)} Calculated from AUC_{corr}

^{c)} Standardized dosing days were 0, 7, 14, 21, 28, and 35

^{d)} t, which varied between doses and days, can be obtained from Appendix 1

(Excerpted from the submission)

Dosing Solution Analysis

Concentration and Stability

Stability was confirmed in standard storage buffer for daratumumab in (b) (4) sodium acetate, (b) (4) sodium chloride, (b) (4) mannitol, (b) (4) % polysorbate 20, pH 5.5. formulations at nominal concentrations of 2-15 mg/mL in room temperature storage for 48 hours and stable for use for up to 5 months. The mean concentrations of daratumumab in solution analyzed during the study were within acceptability criteria of ±15% of nominal concentrations, indicating accurate formulation.

Table 14. Dosing solution for daratumumab for repeat dose toxicology study in chimpanzees

Estimated Protein Concentration of HuMax-CD38 Dose Formulations Using the BCA™ Protein Assay Kit

Animal No. 96A009 Group 1 (5mg/kg HuMax-CD38)				Pre-infusion Dose Solution			Post-infusion Dose Solution		
Time Point	Body Wgt (kg)	Target Concentration		Mean Measured Concentration		% Target Value	Mean Measured Concentration		% Target Value
		mg/ml	mg/kg	mg/ml	mg/kg ⁽¹⁾		mg/ml	mg/kg ⁽¹⁾	
Day 0	55	0 ⁽²⁾	0	0.0006	0	NA	0.0004	0	NA
Day 7	54.6	2.73	5	2.85	5.22	104	2.79	5.11	102
Day 14	54	2.7	5	2.75	5.18	102	2.79	5.16	103
Day 21	53	2.7	5	2.83	5.24	105	2.78	5.15	103
Day 28	53	2.7	5	2.8	5.18	104	2.7	5.0	100
Day 35	53	2.7	5	2.6	4.81	96.3	2.7	5.0	100
Day 42	54	2.7	5	2.9	5.37	107	2.8	5.18	104
Animal No. 95A015 Group 1 (5mg/kg HuMax-CD38)									
Day 0	46	0 ⁽²⁾	0	0.0006	0	NA	0.0004	0	NA
Day 7	43.8	2.19	5	2.29	5.2	105	2.27	5.18	104
Day 14	44.1	2.21	5	2.36	5.34	107	2.35	5.32	106
Animal No. 96A015 Group 2 (25mg/kg HuMax-CD38)									
Day 7	52	0 ⁽²⁾	0	0.0056	0	NA	0.0046	0	NA
Day 21	N/A	0.1 ⁽³⁾	N/A	0.120	N/A	120	0.108	N/A	108
Day 22	51	12.8	25	13.6	26.5	106	14.8	28.9	116
Day 28	50	12.5	25	13.4	26.8	107	13.7	27.5	110
Day 35	49	12.3	25	13.6	27.6	111	13	26.5	106
Day 42	49	12.3	25	13	26.4	106	13.1	26.7	107
Day 49	49	12.3	25	13.3	27.0	108	13.4	27.2	109
Day 56	47.5	11.9	25	11.3	23.7	95	11.9	25	100
Animal No. 96A017 Group 2 (25mg/kg HuMax-CD38)									
Day 7	40	0 ⁽²⁾	0	0.0054	0	N/A	0.0056	0	NA
Day 21	N/A	0.1 ⁽³⁾	N/A	0.124	N/A	124	0.117	N/A	117
Day 22	39	9.8	25	11	28.0	112	11.6	29.6	118
Day 28	38	9.5	25	10.2	26.8	108	10.3	27.1	108
Day 35	38	9.5	25	10.4	27.3	109	10.3	27.1	108
Day 42	38	9.5	25	10.2	26.8	107	10.1	26.5	106
Day 49	39	9.8	25	10.7	27.3	109	10.5	26.7	107
Day 56	38.8	9.7	25	8.1 ⁽⁴⁾	20.8	83.5	8.5	21.9	87.6
Animal No. 92A016 Group 1 (replacement) (5mg/kg HuMax-CD38)									
Day 28	54	0 ⁽²⁾	0	0.00099	0	NA	0.0015	0	NA
Day 35	52	2.6	5	2.7	5.2	104	2.7	5.2	104

⁽¹⁾ Calculated from measured mg/ml protein concentration of test article

⁽²⁾ Control consisting of HuMax-CD38 Final Formulation Buffer at a volume equivalent to the calculated mg/kg HuMax-CD38 (5 mg/kg or 25 mg/kg) dose in saline

⁽³⁾ Priming dose of 100 ml containing 10 mg HuMax-CD38 independent of body weight

⁽⁴⁾ Pre-infusion sample was accidentally diluted causing a lower than expected result; reference Protocol Deviation Number 4 for documentation.

Study title: Pilot Toxicology and Pharmacokinetic Study in Cynomolgus Monkeys with a Two Month Recovery Period

The following study was initially reviewed under IND100638 by Stacey Ricci PhD and parts of it were reformatted to fit this NDA review.

Study no.: 509809
Study report location: eCTD 4.2.3.2
Conducting laboratory and location: [REDACTED] (b) (4)
Date of study initiation: December 21 2005
GLP compliance: Non-GLP
QA statement: Not included
Drug, lot #, and % purity: HuMab-CD38 [REDACTED] (b) (4), lot # 856-018-EP, 99 %

Key Study Findings

- There were no mortalities during the study.
- Significant hematology findings included low- to severe-grade anemia.
- Histopathology findings included lymphoid atrophy and depletion in the thymus, mandibular and mesenteric lymph nodes, spleen and peyers patch, spinal cord myelitis during the main study, and inflammatory cell infiltrates found in spinal cord and sciatic nerves present in recovery animals.

Methods

Doses: 0, 20, 100 mg/kg
 Frequency of dosing: Once weekly (two doses total)
 Route of administration: Intravenous injection (tail vein or left or right saphenous vein)
 Dose volume: 10 mL/kg
 Formulation/Vehicle: (b) (4) sodium phosphate and (b) (4) sodium chloride, pH (b) (4)
 Species/Strain: Cynomolgus monkey
 Number/Sex/Group: 1/sex/group, 1/sex/recovery (8 week recovery period)
 Age: 12 to 18 months old
 Weight: Males 2.2 and 2.4 kg, females 1.8 and 2.0 kg
 Satellite groups: N/A
 Unique study design: N/A
 Deviation from study protocol: None impacted study results or objectives

Table 15. Study design for repeat dose toxicity study in cynomolgus monkey

Group	Treatment (mg/kg)	Concentration (mg/mL)	Animal Designation	Animal	
				Males	Females
1	0	0	Main Study	1	7
			Recovery	2	8
2	20	2	Main Study	3	9
			Recovery	4	10
3	100	10	Main Study	5	11
			Recovery	6	12

(Excerpted from the submission)

Observations and Results**Mortality**

There were no mortalities during the study.

Clinical Signs

Unremarkable

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Ophthalmoscopy

Unremarkable

ECG

Unremarkable; additional cardiovascular parameters included body temperature and heart rate.

Hematology**Table 16. Hematology findings from repeat dose toxicity study in cynomolgus monkey**

Hematology parameter	% change from control							
	Males				Females			
Sex								
Daratumumab (mg/kg)	20	20	100	100	20	20	100	100
Animal #	3	4	5	6	9	10	11	12
Hemoglobin (g/dL)								
Main study Day 11	-21	n/a	-19	n/a	-22	n/a	-20	n/a
Recovery Day 28	n/a	-9	n/a	-43	n/a	-5	n/a	-20
Recovery- Day 64	n/a	-3	n/a	-9	n/a	-2	n/a	-3
Hematocrit (%)								
Main study Day 11	-20	n/a	-20	n/a	-43	n/a	-18	n/a
Recovery Day 28	n/a	-10	n/a	-42	n/a	-7	n/a	-13
Recovery- Day 64	n/a	-9	n/a	-12	n/a	-6	n/a	1
RBC (10⁶/mm³)								
Main study Day 11	-25	n/a	-22	n/a	-52	n/a	-15	n/a
Recovery Day 28	n/a	-20	n/a	-50	n/a	-7	n/a	-22
Recovery- Day 64	n/a	-7	n/a	-13	n/a	-2	n/a	-12
Reticulocytes (10³/mm³)								
Main study Day 11	184	n/a	95	n/a	604	n/a	33	n/a
Recovery Day 28	n/a	0	n/a	174	n/a	25	n/a	517
Recovery- Day 64	n/a	-75	n/a	-70	n/a	-29	n/a	0

Special Evaluation-Flow Cytometry

Peripheral blood

Table 17. Flow cytometry analysis of peripheral blood from repeat dose toxicity study in cynomolgus monkey

FACs analysis	% change from control populations (0 mg/kg)							
Sex	Males				Females			
Daratumumab (mg/kg)	20	20	100	100	20	20	100	100
Animal #	3	4	5	6	9	10	11	12
CD38+ CD4 T cells								
Main study Day 11	-89	n/a	-91	n/a	-96	n/a	-98	n/a
Recovery Day 28	n/a	-86	n/a	-99	n/a	-67	n/a	-91
Recovery- Day 64	n/a	-48	n/a	-61	n/a	-13	n/a	-26
CD38+ CD8 T cells								
Main study Day 11	-80	n/a	-96	n/a	-88	n/a	-99	n/a
Recovery Day 28	n/a	-71	n/a	-99	n/a	-47	n/a	-78
Recovery- Day 64	n/a	-53	n/a	-64	n/a	54	n/a	262
CD38- CD4 T cells								
Main study Day 11	-73	n/a	-76	n/a	-93	n/a	-92	n/a
Recovery Day 28	n/a	-72	n/a	-95	n/a	-64	n/a	-72
Recovery- Day 64	n/a	2	n/a	-68	n/a	-10	n/a	55
CD38- CD8 T cells								
Main study Day 11	-59	n/a	-85	n/a	-92	n/a	-92	n/a
Recovery Day 28	n/a	-36	n/a	-86	n/a	-35	n/a	28
Recovery- Day 64	n/a	-4	n/a	-33	n/a	77	n/a	553
CD38+ NK cells								
Main study Day 11	-98	n/a	-100	n/a	-100	n/a	-100	n/a
Recovery Day 28	n/a	-100	n/a	-100	n/a	-94	n/a	-99
Recovery- Day 64	n/a	-77	n/a	-99	n/a	-15	n/a	-90
CD38- NK cells								
Main study Day 11	-98	n/a	-100	n/a	-100	n/a	-100	n/a
Recovery Day 28	n/a	-100	n/a	-100	n/a	-94	n/a	-99
Recovery- Day 64	n/a	-78	n/a	-99	n/a	-15	n/a	-80
Memory B cells (CD21+CD40+ CD20+)								
Main study Day 11	-97	n/a	-98	n/a	-98	n/a	-98	n/a
Recovery Day 28	n/a	-88	n/a	-100	n/a	-75	n/a	-95
Recovery- Day 64	n/a	-27	n/a	-62	n/a	-15	n/a	-33
CD38 expressing memory B cells (CD27-CD38+CD20+)								
Main study Day 11	-95	n/a	-99	n/a	-97	n/a	-98	n/a
Recovery Day 28	n/a	-31	n/a	-96	n/a	-72	n/a	-92
Recovery- Day 64	n/a	-17	n/a	-36	n/a	-38	n/a	-28

Lymph Node

Minimal depletion of CD38 + and – T CD8 T cells in lymph nodes.

Bone Marrow

Monocytes and NK cells were uninterpretable due to low cell number. B cells were unremarkable

Clinical Chemistry

Table 18. Clinical chemistry findings from repeat dose toxicity study in cynomolgus monkey

Clinical chemistry parameter	% change from control							
	Males				Females			
Sex								
Daratumumab (mg/kg)	20	20	100	100	20	20	100	100
Animal #	3	4	5	6	9	10	11	12
IgG								
Main study Day 11	-50	n/a	-47	n/a	-15	n/a	-20	n/a
Recovery Day 28	n/a	-18	n/a	-71	n/a	-3	n/a	-53
Recovery- Day 64	n/a	-10	n/a	-8	n/a	-18	n/a	-24
IgM								
Main study Day 11	-52	n/a	-41	n/a	-31	n/a	47	n/a
Recovery Day 28	n/a	-42	n/a	-81	n/a	-65	n/a	-77
Recovery- Day 64	n/a	-37	n/a	-52	n/a	-75	n/a	-75
total bilirubin								
Main study Day 11	60	n/a	16	n/a	779	n/a	293	n/a
Recovery Day 28	n/a	24	n/a	43	n/a	9	n/a	0
Recovery- Day 64	n/a	-51	n/a	-38	n/a	-40	n/a	-33

Urinalysis

Unremarkable

Gross Pathology

In both animals at 100 mg/kg, small thymus was observed. There were no changes observed at recovery.

Organ Weights

Both main study animals receiving high dose (100 mg/kg) showed absolute changes in thymus weight and changes in thymus weight relative to body weight (Animal # 5, male 11, female). No changes in thymus weight were observed in recovery animals.

Table 19. Organ weight changes in repeat dose toxicity study in cynomolgus monkey

Organ weight change	% change from control	
	Male	Female
Sex	Male	Female
Daratumumab (mg/kg)	100	100
Animal #	5	11
Absolute thymus weight		
Main study	-46	-82
Thymus % BW		
Main study	-48	-79

%BW, percent body weight

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings:

Table 20. Histological findings in repeat dose toxicity study in cynomolgus monkeys

Treatment related microscopic findings								
Sex			Males			Females		
Daratumumab (mg/kg)			0	20	100	0	20	100
Number of animals examined			1	1	1	1	1	1
Organ	Finding							
Thymus		2					1	
		3		1				
		4			1			1
Mandibular lymph nodes	lymphoid depletion	2			1			
Mesenteric lymph nodes	lymphoid depletion	2			1			
Spleen	lymphoid atrophy	1					1	
		2			1			1
Peyers patch	lymphoid atrophy	2		1				
		3			1			
Spinal cord	inflammation multifocal, cervical	2						1

1 minimal, 2 mild, 3 moderate, 4 severe

Table 21. Histological findings in repeat dose toxicity study in cynomolgus monkeys- recovery

Treatment related microscopic findings							
Sex		Males			Females		
Daratumumab (mg/kg)		0	20	100	0	20	100
Number of animals examined		1	1	1	1	1	1
Organ	Finding						
Spinal cord	inflammatory cell infiltration	1		1	1		
Sciatic nerve	inflammatory cell infiltration	1			1		
Lymph node, mesenteric	lymphoid depletion	1			1		
Thymus	atrophy	1					1
Spleen	adhesions					1	

1 minimal, 2 mild, 3 moderate, 4 severe

Bone marrow smears showed an increase in normoblasts in 3 animals. On Day 11, all treated animals showed a lymphopenia. Bone marrow returned to normal by end of recovery.

Special Evaluation- Immunogenicity

Development and validation of ELISA methodology to detect cynomolgus antibodies to HuMab-CD38: Study #259477

Methods

Immune response was defined by greater than 4-fold increase over the initial titre, at various time points.

Results

A positive immune response was observed towards the end of the study in two of four animals (main and recovery) receiving 20 mg/kg.

Toxicokinetics

- HuMab-CD38 exposure increased proportionally in males and slightly supra-proportionally in females with increasing dose on Day 1
- There were no apparent differences in exposure when comparing Days 1 and 8 in both C_{max} and AUC (>2 fold)
- The T_{max} for HuMab-CD38 was between 0.5 and 3.5 hours

- The $T_{1/2}$ for HuMab-CD38 was between 9 and 63 hours.
- HuMab-CD38 exposure was similar between male and female monkeys (Cmax and AUC)

Table 22. Toxicokinetic summary for repeat dose toxicity summary in cynomolgus monkeys on Day 1

Table 1
Toxicokinetic Parameters of HuMab-CD38 in Male Monkey Serum
Following Intravenous Infusion of 20 or 100 mg/kg HuMab-CD38 on Day 1

Sex	Dose (mg/kg)	Group/ Animal	Cmax (ng/mL)	Tmax (h)	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	T1/2 (h)	Kel (1/h)	CL (mL/h/kg)	Vd (mL/kg)	Vss (mL/kg)	Vcen (mL/kg)
Male	20	Main 3M	1920000	3.50	35452600	NR	NR	NR	NR	NR	NR	33.00
		Rec 4M	682000	2.00	29122350	34387345	62.92	0.01102	0.5816	52.80	51.14	53.05
		n	2	2	2	1	1	1	1	1	1	2
		Mean	1300000	2.75	32287475	34387345	62.92	0.01102	0.5816	52.80	51.14	43.03
		SD	-	-	-	-	-	-	-	-	-	-
	100	Main 5M	2880000	0.50	138086500	NR	NR	NR	NR	NR	NR	34.72
		Rec 6M	3760000	3.50	237890000	NR	NR	NR	NR	NR	NR	35.34
		n	2	2	2	0	0	0	0	0	0	2
		Mean	3320000	2.00	187988250	-	-	-	-	-	-	35.03
		SD	-	-	-	-	-	-	-	-	-	-
Female	20	Main 9F	416000	1.00	21807850	24555785	48.22	0.01437	0.8145	56.66	61.91	59.17
		Rec 10F	498000	3.50	33319250	NR	NR	NR	NR	NR	NR	60.06
		n	2	2	2	1	1	1	1	1	1	2
		Mean	457000	2.25	27563550	24555785	48.22	0.01437	0.8145	56.66	61.91	59.62
		SD	-	-	-	-	-	-	-	-	-	-
	100	Main 11F	2880000	3.50	196521500	NR	NR	NR	NR	NR	NR	41.84
		Rec 12F	3980000	0.50	189266500	NR	NR	NR	NR	NR	NR	25.13
		n	2	2	2	0	0	0	0	0	0	2
		Mean	3430000	2.00	192894000	-	-	-	-	-	-	33.48
		SD	-	-	-	-	-	-	-	-	-	-

NR Not Reported, the coefficient of determination was less than 0.800 and/or the extrapolation of the AUC to infinity represented more than 20% of the total area.

(Excerpted from the submission)

Table 23. Toxicokinetic summary for repeat dose toxicity summary in cynomolgus monkeys on Day 8

Toxicokinetic Parameters of HuMab-CD38 in Male Monkey Serum
Following Intravenous Infusion of 20 or 100 mg/kg HuMab-CD38 on Day 8

Sex	Dose (mg/kg)	Group/ Animal	Cmax (ng/mL)	Tmax (h)	AUC(0-t) (ng.h/mL)	AUC(0-inf) (ng.h/mL)	T1/2 (h)	Kel (1/h)	CL (mL/h/kg)	Vd (mL/kg)	Vss (mL/kg)	Vcen (mL/kg)	
Male	20	Main 3M	707000	0.50	19698100	NR	NR	NR	NR	NR	NR	28.29	
		Rec 4M*	815000	0.50	43435508	43443019	12.92	0.05366	0.4604	8.580	30.43	24.54	
	100	Main 5M	3810000	2.00	101670750	NR	NR	NR	NR	NR	NR	36.10	
		Rec 6M	3460000	0.50	403617384	403619802	22.20	0.03122	0.2478	7.935	35.28	28.90	
	Female	20	Main 9F	481000	1.00	14784875	NR	NR	NR	NR	NR	NR	45.66
			Rec 10F*	558000	12.50	32000906	32003531	9.38	0.07391	0.6249	8.455	24.15	38.76
100		Main 11F	3880000	0.50	110092250	NR	NR	NR	NR	NR	NR	25.77	
		Rec 12F	3820000	2.00	703593130	703595042	30.12	0.02301	0.1421	6.176	26.14	41.15	

NR Not Reported, coefficient of determination was less than 0.800 and/or the extrapolation of the AUC to infinity was more than 20% of the total area. Animals 4M and 10F were considered to exhibit a positive antibody response and therefore estimates were excluded from interpretation.

(Excerpted from the submission)

Dosing Solution Analysis

No formulation analysis was conducted.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Studies not conducted.

7.2 *In Vitro* Assays in Mammalian Cells

Studies not conducted.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Studies not conducted.

7.4 Other Genetic Toxicity Studies

Studies not conducted.

8 Carcinogenicity

Studies not conducted.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Studies not conducted.

9.2 Embryonic Fetal Development

Studies not conducted.

9.3 Prenatal and Postnatal Development

Studies not conducted.

10 Special Toxicology Studies

None submitted to the BLA.

11 Integrated Summary and Safety Evaluation

The nonclinical studies submitted to this BLA provide sufficient information to support the approval of Darzalex (daratumumab) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Daratumumab is human anti-CD38 monoclonal antibody. In vitro pharmacology studies show daratumumab can induce tumor cell lysis through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) in malignancies expressing CD38. Daratumumab also promotes apoptosis in vitro through Fc mediated cross-linking.

Pharmacology studies also indicate daratumumab modulates CD38 enzyme activity through inhibition of ribosyl cyclase enzyme activity and stimulation of the cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of CD38, whereas the surrogate HuMab-3003-003 ability to inhibit ribosyl cyclase enzyme activity is substrate dependent and it conversely inhibits cADPR hydrolase activity. Importantly, the degrees to which the known mechanisms contribute to the clinical efficacy of daratumumab is still unknown. In vitro evidence suggests the main difference between daratumumab and the HuMab-CD38 is the loss of CDC activity and the differences in their modulation of CD38 enzymatic activity. In vivo, daratumumab reduces tumor growth and burden in human lymphoma xenograft mouse models relative to isotype specific control antibody. Based on the nonclinical data submitted in the BLA and its chemical structure, the Established Pharmacological Class (EPC) of “human CD38-directed monoclonal antibody” was determined to be both clinically meaningful and scientifically valid for idarucizumab.

Stand-alone safety pharmacology studies were not conducted, however ECG parameters, respiratory rates, body temperatures and pulse rates were assessed during the 6 week repeat dose toxicology study in chimpanzees and were unremarkable at doses up to 25 mg/kg. In addition, ECG parameters, body temperatures and heart rates were assessed during the 2-week repeat-dose toxicology study in monkeys and were unremarkable at doses up to 100 mg/kg.

Based on the data collected in general toxicology studies, there were no gender differences in exposure in either chimpanzees or monkeys. In chimpanzees increased C_{max} and AUC values were greater than dose proportional and approximately dose proportional in monkeys. Daratumumab was slowly eliminated in the blood following intravenous dosing with half-lives of approximately 15.5-18.8 days in chimpanzees and 9-63 hours for the surrogate HuMab-CD38 antibody in the monkey.

The general toxicology studies were conducted in the chimpanzee and monkey via IV, which is the intended route of administration. Nonclinical findings show toxicities of daratumumab or the surrogate HuMab-CD38 consistently in the hematopoietic and lymphatic systems. The most obvious toxicity observed was cytokine release syndrome which resulted in mortality in the chimpanzee study. Additionally toxicities were noted in the liver, spinal cord/nervous system. Hematology findings from the 6 week study in chimpanzees and the 2 week study in monkeys included decreases in red blood cells, hemoglobin, hematocrit, white blood cells, and platelets. Histopathology findings in the lymphoid organs included lymphoid depletion and atrophy in the thymus, mesenteric and mandibular lymph nodes, spleen and peyers patch.

The Applicant did not conduct genotoxicity, reproductive and developmental toxicology studies, or carcinogenicity studies with daratumumab. Standard genotoxicity studies are not generally applicable to biotechnology-derived pharmaceuticals (per ICH S6) and were not needed. The considerations led to no reproductive and developmental toxicology studies being conducted for daratumumab include: the lack of a pharmacologically relevant species for testing (aside from the chimpanzee wherein these studies are not feasible); that these studies are not warranted to support

marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (per ICH S9); and that the patient population is generally beyond reproductive age. ICH S9 also outlines that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, and as such no carcinogenicity studies were needed.

12 Appendix/Attachments

None.

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/s/

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10/20/2015

CHRISTOPHER M SHETH
10/20/2015