WINSHIP CANCER INSTITUTE OF EMORY UNIVERSITY
INVESTIGATOR-INITIATED STUDY
WITH
MILLENNIUM PHARMACEUTICALS
INVESTIGATIONAL AGENT: IXAZOMIB

CLINICAL STUDY PROTOCOL

Takeda Oncology Clinical Study Protocol X16071
Phase 0 Analysis of Ixazomib (MLN9708) in Patients with Glioblastoma

Indication: Glioblastoma
Phase: Phase 0

Protocol History

Draft	26 Jan 2015
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This is an investigator-initiated study. The principal investigator, Jeffrey J. Olson (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: Phase 0 Analysis of Ixazomib (MLN9708) in Patients with Glioblastoma

Phase: 0

Number of Patients: 3

Study Objectives

Primary

1. Measurement of tissue concentration of ixazomib in a glioblastoma after preoperative administration
2. Measurement of blood and plasma concentration of ixazomib during surgical sampling after preoperative administration

Secondary

1. Assessment of the safety of ixazomib after single dose administration in glioblastoma patients undergoing surgery for tissue concentration assessment.

Overview of Study Design:

This is a surgically based Phase 0 study of MLN9708 administration in 3 patients to determine whether its active metabolite MLN2238 can be measured in tumor in individuals with glioblastoma. The primary endpoint centers around MLN2238 concentration measurements in the glioblastoma, blood and plasma of these individuals 3 hours after administration.

Study Population:

Patients with recurrent glioblastoma requiring surgery will be candidates for this study. The specific criteria are as follows:

Key Inclusion Criteria

1. Age 18 or above
2. Recurrent glioblastoma for which surgical resection is indicated
3. Karnofsky Performance Status of 60 or above
4. Platelet count > 100,000
5. ANC > 1,500
6. Hemoglobin > 9 g/dL
7. LFTs < 3 x Upper Limit of Normal for the testing lab
8. Creat < 1.5 mg/dL

Key Exclusion Criteria

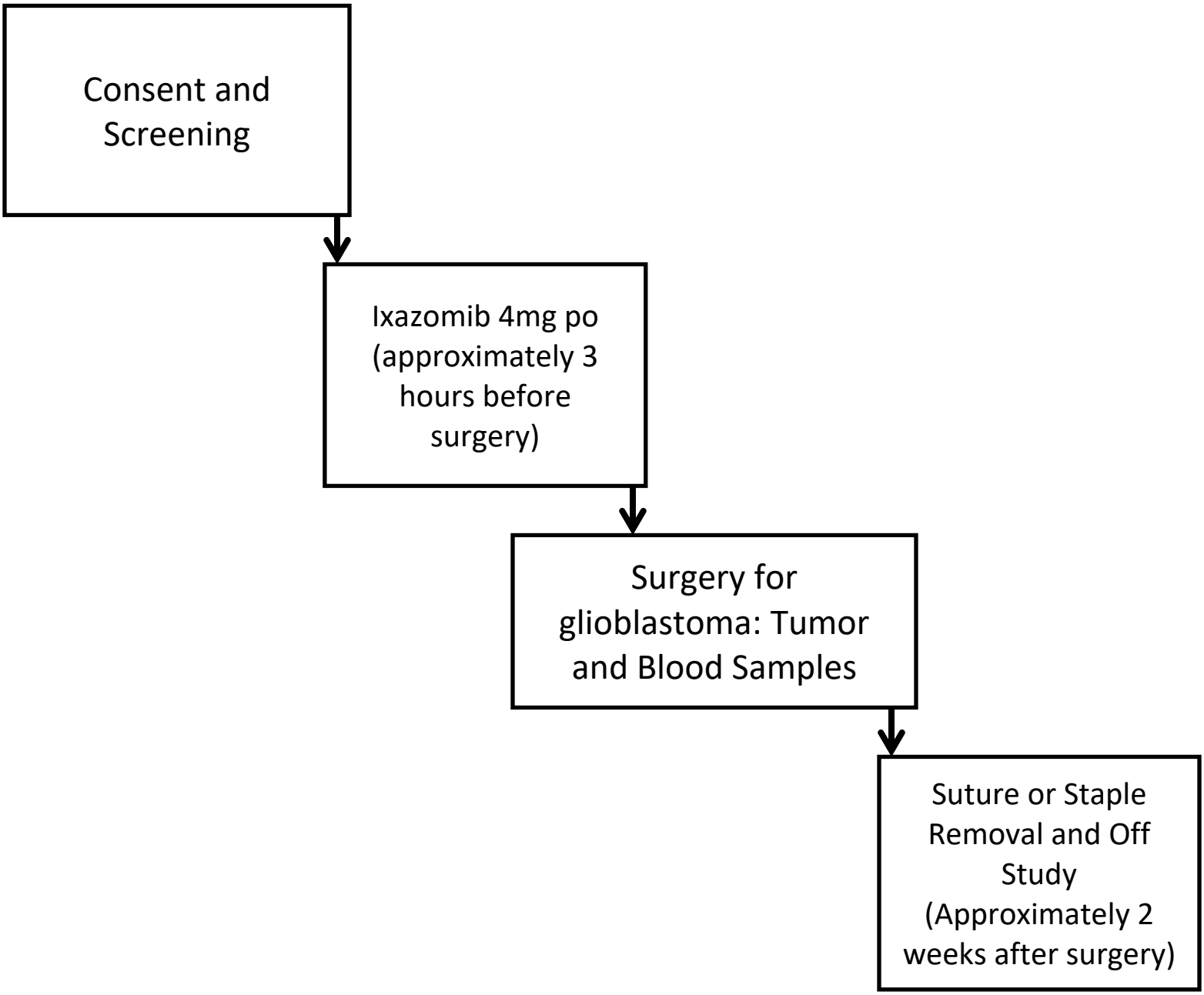
1. Grade ≥ 3 peripheral neuropathy or Grade 2 with pain on clinical examination during the screening period.

Duration of Study:

Each individual will begin study activity at the time of Ixazomib administration 3 hours pre-operatively until about two weeks post-operatively when their staples or sutures are removed. It is estimated one subject will be accrued every two months. Thus the study duration will be

approximately 6 months. (please note that all serious adverse events must be reported up to 30 days after the dose of ixazomib as described in Section 8.2: Procedures for Reporting Serious Adverse Events).

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

Outline of Events

I. Informed consent process completed
II. Laboratory screening to confirm or deny eligibility
III. Ixazomib administration 3 hours prior to surgery
IV. Surgical resection of tumor
    A. Tumor specimen collection for MLN2238 concentration assessment
    B. Timed blood specimen collection during surgery for MLN2238 concentration assessment
V. Off-study assessment at the time of suture or staple removal

Safety of ixazomib administration will be assessed from the first administration of ixazomib until approximately 2 weeks post-operatively. Attributions of adverse events will be determined and recorded by likely source of that event.

Schedule of Events and Observations

	Consent	Screening	Ixazomib Administration 3 Hours Before Surgery	Surgery	Postop Day 1	Postop Visit for Staple/Suture Removal
Reference Time Line	14 or fewer days before date of surgery	After consent and prior to ixazomib administration	1 to 3 hours prior to surgical incision	On average a two to four hour period of time with sampling occurring as clinically safe during the tumor resection	Assessment 12 to 36 hours after the end of the surgery	Depending on the nature of the wound repair and integrity staple/suture removal will occur 10 to 20 days after the day of surgery
Patient Education	**x**					
Laboratory screening		**x**				
Observation for clinical and laboratory toxicity using standard postop parameters*			**x**		**x**	**x**
Blood sampling just prior to incision				**x**		
Blood sampling during tumor sampling				**x**		
Blood sampling during surgical closure				**x**		
Tumor sampling				**x**		
*** Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.**						

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CFR	Code of Federal Regulations
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration

Abbreviation	Term
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	cardiovascular
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene

Abbreviation	Term
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression) Progressive disease
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome

Abbreviation	Term
PSA	prostate-specific antigen
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Glioblastoma, the most common primary tumor of the brain in adults, is rarely associated with cure or even control.[1] Advances in surgical care and radiation planning have improved safety, and the addition of temozolomide to initial therapy has added some months to overall survival.[2]

At progression bevacizumab extends time to further imaging progression, but not overall survival. Having said this, average overall survivals are still in the range of 12-14 months. This clearly leaves room for improvement by exploring other therapeutic modalities. Standard cytotoxic agents have been studied from a number of standpoints and their effect has probably been maximized.[3, 4, 5]

Bortezomib, a proteasome inhibitor, has been evaluated in preclinical and clinical studies with promising results, as a single agent or in combination with temozolomide and radiation therapy. As a single agent at recurrence, partial responses have been observed.[6] Additionally, bortezomib appears to enhance radiation effects in these tumors [7, 8]. In a phase I study of 66 patients with primarily recurrent glioblastoma the maximum tolerated dose in those not taking enzyme-inducing anti-seizure drugs was 1.70 mg/ m^2 based on grade 3 thrombocytopenia, sensory neuropathy and fatigue. In the group taking enzyme-inducing anti-seizure drugs escalation was terminated at 2.5 mg/m^2 without meeting meet the maximum tolerated dose criteria. However, proteasome inhibition in this group did not change at significantly at doses above 1.50 mg/m^2 for those not taking enzyme-inducing anti-seizure drugs and above 1.90 mg/m^2 for those taking enzyme-inducing anti-seizure drugs. This suggests that further escalations beyond those studied in this protocol would be unlikely to increase the biologic effect of this proteasome inhibitor. Two partial responses were observed.[9] Based on this information there appears to be a potential role for proteasome inhibitors in the management of progressive glioblastoma and this warrants the investigation at hand here.=.

1.1.2 Ixazomib (MLN9708)

1.2 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.3 Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with Revlimid and Dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of RRMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and

severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

1.4 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days [10]. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA [11]. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK doses of ixazomib.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

1.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma) have been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

Table Error! No text of specified style in document.-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W
C16010 RRMM N = 200	PO, W, with LenDex versus placebo-LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM	PO, W, with LenDex	4.0 mg W

Table Error! No text of specified style in document.-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
N = 9		
C16014 Symptomatic MM N=701	PO, combination with LenDex	ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: ixazomib 3.0 mg on Day 1 Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle
C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB-MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

Abbreviations: RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or refractory systemic light chain amyloidosis RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

a Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m^2 BSA dosing.

Overview of the Oral Formulation of Ixazomib

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Overall Safety Population: Treatment-Emergent Adverse Events Reported by ≥ 10% of Patients

Primary System Organ Class Preferred Term	IV Studies[a] N = 146	Oral Studies[b] N = 491	Total N = 637
Subjects With at Least 1 TEAE	145 (99)	482 (98)	627 (98)
Gastrointestinal disorders	**115 (79)**	**400 (81)**	**515 (81)**
Nausea	59 (40)	230 (47)	289 (45)
Diarrhoea	51 (35)	230 (47)	281 (44)
Vomiting	60 (41)	181 (37)	241 (38)
Constipation	36 (25)	134 (27)	170 (27)
Abdominal pain	28 (19)	60 (12)	88 (14)
General disorders and administration site conditions	**118 (81)**	**363 (74)**	**481 (76)**
Fatigue	89 (61)	223 (45)	312 (49)
Pyrexia	45 (31)	112 (23)	157 (25)
Oedema peripheral	31 (21)	122 (25)	153 (24)
Asthenia	10 (7)	74 (15)	84 (13)
Nervous system disorders	**87 (60)**	**272 (55)**	**359 (56)**
Dizziness	25 (17)	85 (17)	110 (17)
Headache	31 (21)	74 (15)	105 (16)
Neuropathy peripheral	17 (12)	81 (16)	98 (15)
Metabolism and nutrition disorders	**89 (61)**	**267 (54)**	**356 (56)**

Decreased appetite	56 (38)	120 (24)	176 (28)
Dehydration	25 (17)	61 (12)	86 (14)
Primary System Organ Class	**IV Studies[a]**	**Oral Studies[b]**	**Total**
Hypokalaemia	11 (8)	57 (12)	68 (11)
Blood and lymphatic system disorders	**88 (60)**	**256 (52)**	**344 (54)**
Thrombocytopenia	65 (45)	161 (33)	226 (35)
Anaemia	28 (19)	114 (23)	142 (22)
Neutropenia	16 (11)	103 (21)	119 (19)
Lymphopenia	16 (11)	61 (12)	77 (12)
Skin and subcutaneous tissue disorders	**84 (58)**	**255 (52)**	**339 (53)**
Rash (all terms)	73 (50)	197 (40)	270 (42)
Rash maculo-papular	21 (14)	60 (12)	81 (13)
Rash macular	15 (10)	56 (11)	71 (11)
Musculoskeletal and connective tissue disorders	**78 (53)**	**249 (51)**	**327 (51)**
Back pain	27 (18)	88 (18)	115 (18)
Arthralgia	17 (12)	72 (15)	89 (14)
Pain in extremity	21 (14)	66 (13)	87 (14)
Respiratory, thoracic and mediastinal disorders	**87 (60)**	**228 (46)**	**315 (49)**
Cough	32 (22)	94 (19)	126 (20)
Dyspnoea	31 (21)	80 (16)	111 (17)
Infections and infestations	**48 (33)**	**244 (50)**	**292 (46)**
Upper respiratory tract infection	12 (8)	94 (19)	106 (17)
Psychiatric disorders	**32 (22)**	**151 (31)**	**183 (29)**
Insomnia	14 (10)	89 (18)	103 (16)

Source: \biostatistics\MLNM9708\IB\2014\Tables\T14.1.3-TEAE_Pct10_Pooled and \biostatistics\MLNM9708\IB\2014\Tables\T14.6.2-TEAE_AESI_Rash; data cutoff 27 March 2014.
Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug.
A subject counts once for each preferred term and system organ class. Percentages use the number of treated subjects as the denominator.
[a] Studies C16001 and C16002.
[b] Studies C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16013, C16015, C16017, C16018, and TB-MC010034.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhoea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Oedema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalaemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anaemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular[a]	29 (17)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Dyspnoea	26 (15)

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

Data from ongoing blinded pivotal trials (C16010) are not included.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash..

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors [12], non-Hodgkin's disease, Hodgkin's disease [13], relapsed and/or refractory multiple myeloma [RRMM; , 14, 15], relapsed or refractory systemic light chain amyloidosis [RRAL; 16], and newly diagnosed multiple myeloma [NDMM; 17, 18, 19]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

1.6 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.(, 20, 21) Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM.(22, 23,

24) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were to be enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Final study results are currently being analyzed, but preliminary data suggest that ixazomib has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the ixazomib IB and SMA for further information.

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are phase 1/2, with phase 1 focusing on safety and phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

1.8 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.9 Study Rationale

Glioblastoma, the most common primary tumor of the brain in adults, is rarely associated with cure or even control. Advances in surgical care and radiation planning have improved safety, and the addition of temozolomide to initial therapy has added some months to overall survival. At progression bevacizumab extends time to further imaging progression, but not overall

survival. Having said this, average overall survivals are still in the range of 12-14 months. This clearly leaves room for improvement by exploring other therapeutic modalities. Standard cytotoxic agents have been studied from a number of standpoints and their effect has probably been maximized.

Thus, alternative agents, either targeted to critical pathways related to tumor growth, or interrupting normal tumor cellular metabolism provide promising alternatives. One of these strategies is altering the normal function of the 20S proteasome subunit. Ixazomib has a shorter 20S proteasome dissociation half-life than bortezomib, which plays an important role in improving tissue distribution. Direct comparison with bortezomib has revealed that Ixazomib has an improved pharmacokinetic and pharmacodynamic profile and shows superior antitumor activity in both solid tumor and hematologic xenograft models, and shows antitumor activity when administered via multiple dosing routes and regimens. Although bortezomib has not been shown to have single agent efficacy in glioblastomas, the characteristics of ixazomib may be advantageous. It has not been determined as to whether or not the active metabolite of ixazomib reaches these tumors effectively. Preclinical models of glioblastoma, though very interesting, do not easily recapitulate the human situation in terms of size, tumor heterogeneity or effects of systemic metabolism. In order to address this question directly, a phase 0 study of ixazomib is proposed here to answer this question prior to moving forward with more advanced phase studies.

1.10 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2. STUDY OBJECTIVES

2.1 Primary Objectives

1. Measurement of tissue concentration of ixazomib in a glioblastoma after preoperative administration

2. Measurement of blood and plasma concentration of ixazomib during surgical sampling after preoperative administration

2.2 Secondary Objectives

1. Assessment of the safety of MLN9708 after single dose administration in glioblastoma patients undergoing surgery for tissue concentration assessment.

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Determination of brain tumor tissue, blood and plasma concentrations ixazomib

3.2 Secondary Endpoints

Determination of the safety of MLN9708 after single dose administration in glioblastoma patients undergoing tumor resection

4. STUDY DESIGN

4.1 Overview of Study Design

Individuals who are candidates for surgery for recurrent (or progressive) glioblastoma will be considered for participation in this study. Those deemed by the PI to be potential candidates will be counseled and provided a consent. Those signing a consent will then undergo eligibility screening. Those eligible will receive 4 mg of Ixazomib orally 3 hours prior to surgery and be on study as of that day. Tumor samples will be obtained at the time of surgery and provided to Covance for MLN2238 assay. Also during the surgery, blood samples will be obtained at the time of induction, one and two hours later and provided to Covance for ixazomib assay in both blood and plasma. At the time of return to the outpatient clinic the individual will be assessed for safetyrelated to Ixazomib administration. At that point the individual will be off study. Adverse events are followed and reported for 30 days after drug administration. The subject will continue to follow-up with their surgeon and oncologist as per standard care for their circumstance and therapy dictates and the adverse events will be captured at those follow-up visits.

4.2 Number of Patients

Three patients will be enrolled in this study. Enrollment will commence at the time of Ixazomib administration.

4.3 Duration of Study

This investigation will enroll approximately 1 patient every 2 months with completion expected 6 months after Winship Cancer Center checklists are completed. For the individuals enrolled, study activity will last from the day of surgery until the day the sutures or staples are removed. The average time period for the wound to heal well enough for suture or staple removal is 10-17 days depending on the nature of the surgical wound. (please note that all serious adverse events must be reported up to 30 days after the dose of ixazomib as described in Section 8.2: Procedures for Reporting Serious Adverse Events). The subject will continue to follow-up with their surgeon and oncologist as per standard care for their circumstance and therapy dictates and the adverse events will be captured at those follow-up visits.

4.4 Staggered Enrollment

Patients will be enrolled in a staggered fashion with ≥ 4 weeks between each patient dosed.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.

2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Female patients who:

   - Are postmenopausal for at least 1 year before the screening visit, OR

   - Are surgically sterile, OR

   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR

   - Agree to practice true abstinence when this is in line with the preferred and usual

lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

4. Patients must have a previous diagnosis of a recurrent or progressive glioblastoma for which surgical resection is now indicated.

5. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2 or (Karnofsky Performance Status of 60 or above).

6. Patients must meet the following clinical laboratory criteria:

   - Absolute neutrophil count (ANC) ≥1,500/mm^3 and platelet count ≥100,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
   - Hemoglobin > 9 g/dL
   - Total bilirubin ≤1.5× the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)≤3×ULN for the lab utilized.
   - Creatinine ≤ 1.5 mg/dL
   - Calculated creatinine clearance ≥ 30 mL/min (see Section 11.2).

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or have a positive serum pregnancy test during the

screening period.

2. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy.

3. Major surgery, including craniotomy, within 14 days before enrollment.

4. Radiotherapy of brain tumor within 3 months before enrollment.

5. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

6. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

7. Systemic treatment, within 14 days before the first dose of ixazomib, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

8. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

9. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

10. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

11. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.

12. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

13. Patient has ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical

examination during the screening period.

14. Participation in other clinical trials utilizing other therapeutic investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

15. Patients that have previously been treated with ixazomib, or participated in a study with ixazomib whether treated with ixazomib or not.

6. STUDY DRUG

6.1 Description of Investigational Agents

Ixazomib Capsules
The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green
0.2 mg	Size 4	White opaque

For additional details, please see the ixazomib IB.

6.2 Study Drug Administration

Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.3).

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 0.2-, 0.5-, and 2.0 mg, or as capsules of 2.3-, 3.0- and 4.0 mg ixazomib.

The prescribed administration of the ixazomib dose in this study is one 4.0 mg dose approximately 3 hours prior to surgery. No further doses of ixazomib will be administered. The dose will be dispensed by the Emory University Hospital Research Pharmacy and administered by the PI who will document the time of administration, the dose, and toleration of the dose in the operative dictation. The patient will be in the preoperative waiting room and then the preoperative holding area after administration while being prepared for surgery. As there is only one dose used in this study, and it will be documented as part of the surgical procedure, no drug diary will be used.

Patients will be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) as they will have been NPO since midnight on the day surgery in preparation for general anesthesia. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Ixazomib Destruction

Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

Anesthetic agents, corticosteroids, anticonvulsants, antibiotics and other supportive agents will be administered during and after the surgical procedure (respecting those not allowed in the exclusion criteria list item number 8 above).

6.3 Excluded Concomitant Medications and Procedures

The following medications are prohibited from 14 days prior to the dose of ixazomib to 7 days after the dose of ixazomib, ie. the study period.

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during the study period as these drugs may interfere with the evaluation of the pharmacokinetics of ixazomib:

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin

- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided during the study period, unless there is no appropriate alternative medication for the patient's use as these drugs may interfere with the evaluation of the pharmacokinetics of ixazomib:

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

6.4 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.5 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment with ixazomib.

Pregnancy

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of

reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.6 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated. Other antivirals are also acceptable.

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry

areas of the body or oral or topical antihistamines). A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularlyfollowing administration of ixazomib. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice.

Fluid Deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of ixazomib and as needed during treatment to avoid dehydration.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose

adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of ixazomib and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

6.7 Preparation, Reconstitution, and Dispensing

Ixazomib is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling ixazomib capsules.

6.8 Packaging and Labeling

The study drug ixazomib capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged using cold-form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

6.9 Storage, Handling, and Accountability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

6.10 Study Compliance

Not applicable in this study.

6.11 Study Treatment

Schedule of Events and Observations

	Consent	Screening	Ixazomib Administration 3 Hours Before Surgery	Surgery	Postop Day 1	Postop Visit for Staple/Suture Removal
Reference Time Line	14 or fewer days before date of surgery	After consent and prior to ixazomib administration	1 to 3 hours prior to surgical incision	On average a two to four hour period of time with sampling occurring as clinically safe during the tumor resection	Assessment 12 to 36 hours after the end of the surgery	Depending on the nature of the wound repair and integrity staple/suture removal will occur 10 to 20 days after the day of surgery
Patient Education	**x**					
Laboratory screening		**x**				
Observation for clinical and laboratory toxicity using standard postop parameters*			**x**		**x**	**x**
Blood sampling just prior to incision				**x**		
Blood sampling during tumor sampling				**x**		
Blood sampling during surgical closure				**x**		
Tumor sampling				**x**		
*** Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.**						

Informed Consent Process: Patients with recurrent glioblastoma who need surgery will be presented the concept of this study and its pro's and con's. They will then receive a consent form and be allowed to review it. They will then be allowed to ask questions and provided these are satisfactorily answered sign consent. This process may take one or more days.

Screening: After signing informed consent there will be determination of performance status, CBC, Complete Metabolic Panel, Na/K/Glucose/Chloride/Bun/Cr, PT/PTT/INR, Urinalysis, & Serum pregnancy test.

Ixazomib Administration: 4.0 mg Ixazomib administration orally with 8 oz of water 3 hours prior to projected surgery start time. The individual will be observed for evidence of treatment-emergent adverse events. This will be recorded as the on study time. Accurate recording of the time of ixazomib administration will be made in the patient's clinical records.

Surgery: One red top tube of blood will be collected at the time of surgical incision, tumor sampling and wound closure. The time of each sampling will be recorded. The tumor will sampled at three different sites and the timing of the sampling will be recorded.

Post Op Day 1: General and neurologic exam observations will be collected and laboratory evaluations performed with be collected and recorded.

Post Op Visit for Staple/Suture Removal: The subject will undergo standard staple/suture removal, with observations from the general and neurologic exam being collected for assessment of potential Ixazomib toxicity. The patient will be the off study point and visit (please note that all serious adverse events must be reported up to 30 days after the dose of ixazomib as described in Section 8.2: Procedures for Reporting Serious Adverse Events). The subject will continue to follow-up with their surgeon and oncologist as per standard care for their circumstance and therapy dictates and the adverse events will be captured at those follow-up visits.

6.12 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated
- Other

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF. If the patient is unable have surgery after the drug

administration or us unable to come to the off study suture/staple removal visit they will be withdrawn from the study and replaced until three patient complete follow-up through the off study visit.

7. STATISTICAL AND QUANTITATIVE ANALYSES

7.1 Statistical Methods

This will be a phase 0 study designed to assess whether or not Ixazomib reaches glioblastoma tissue in measurable concentrations. The drug concentration results and clinical observations after administration will be tabulated and summarized with simple descriptive statistics. The relationship between patient's demographic, tumor and drug concentration results will be assessed with Pearson's correlation coefficient and tested with Wald's test. In addition, the mean and standard error of the concentrations will be estimated using a random-effects model to account for the within-patient correlation of the tumor biopsy samples. Given the limited number of observations, a relatively simple covariance matrix (e.g. compound symmetry) will be assumed.

7.1.1 Determination of Sample Size

The sample size will be three cases. This is based on clinical judgment believing this will provided enough data to account for tumor inter-tumor heterogeneity. To assist in addressing tumor heterogeneity three samples from different portions of the tumor will be obtained in each case and their location described in the operative report.

Should a patient fail to be able to take the preoperative Ixazomib dose, undergo the surgery for tumor resection, have useful surgical samples obtained or be unable to reach the postoperative visit for suture/staple removal the patient will be removed from study and a replacement patient will be recruited.

7.1.2 Populations for Analysis

Patients to be enrolled will be have recurrent or progressive glioblastoma for which surgical resection is indicated and have a Karnofsky Performance Status of 60 (ECOG 2) or above.

7.1.3 Procedures for Handling Missing, Unused, and Spurious Data

If there is reason to believe that there is a problem with handling of the tumor specimens likely to render their pharmacokinetic analysis inaccurate the data from this subject will be discarded and a replacement subject recruited. Similarly, if pharmacokinetic or safety data is missing on a subject, and is irretrievable for technical or other reasons, a replacement subject will be recruited.

7.1.4 Demographic and Baseline Characteristics

The baseline clinical observations will be provided with simple descriptive statistics and tables of observations.

7.1.5 Pharmacokinetics/Pharmacodynamics/Biomarkers *(if applicable)*

The primary objective of this study is measurement of tumor tissue concentrations of ixazomib in a glioblastoma after preoperative administration. This will be done in one point in time (during surgery) and from multiple spots in the tumor for each of the three participants. The sample from each site within each tumor will be analyzed separately. These results will allow simple descriptive statistics of the concentration data but no formal pharmacokinetic parameters will be calculated.

7.1.6 Safety Analysis

Safety will be assessed with routine postoperative laboratory, vital sign, neurologic exam, and imaging through the day of staple or suture removal. This data will be collected and any adverse events (as defined below) graded and their relationship to the Ixazomib administration determined.

7.1.7 Adverse Event Stopping Rule

For any toxicity ≥ one grade above baseline for any pre-existing adverse events (AEs), and any new grade ≥ 2 AEs study accrual will be suspended. The study team will review the data to determine the proper course of action. These actions may include further adverse event monitoring and evaluation to assess attribution of the adverse event observed, continued suspension of accrual pending study modification, dose modification, and closure of the trial.

7.1.8 Data Safety Monitoring Plan

Winship Cancer Institute's Data and Safety Monitoring Committee (DSMC) will review toxicity and safety data for each subject following completion of the 2 week post-operative/off-study visit. The sponsor-investigator is responsible for providing adverse event data to the DSMC for review. Should any SAEs occur, from first dose of study drug through 30 days post-administration, the sponsor-investigator will halt enrollment and notify DSMC of event occurrence. Any SAE, regardless of relationship to the study drug, will be reported to the DSMC for review prior to enrollment of subsequent patients to evaluate the safety of trial continuation.

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

8.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves

suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2 Procedures for Reporting Serious Adverse Events

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator, Jeffrey J. Olson, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to Millennium Pharmacovigilance (or designee):

> **Fatal and Life Threatening SAEs** within 24 hours of the sponsor-investigator's observation or awareness of the event
>
> **All other serious (non-fatal/non life threatening) events** within 4 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4.0, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html. [25]
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4.0. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to all study drugs for each SAE will be determined by the investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information

Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

8.3 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Millennium)

9. ADMINISTRATIVE REQUIREMENTS

9.1 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,

- Phone: 1-877-TAKEDA7 (1-877-825-3327)
- E-mail: medicalinformation@tpna.com
- FAX: 1-800-247-8860
- Hours: Mon-Fri, 8 a.m. – 6 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance

10 REFERENCES

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11. APPENDICES

11.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

Karnofsky Performance Status Scale

The following table presents the Karnofsky performance status scale[1]:

Points	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

- [1] Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. *Cancer* 1984;53:2002-2007.

11.2 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

11.3 Pharmacokinetic (PK) Sample Collection and Handling (Mandatory, if Applicable)

Materials and Labeling

Blood samples for PK assessment must be collected in 3-mL Vacutainer tubes containing K2EDTA as the anticoagulant. Resulting blood and plasma PK samples must be stored in plastic storage tubes with caps. No blood collection tubes with separation gel should be used.

Collected tumor samples will be dissected to a size of roughly 200-300 mg. The samples are weighed, wrapped in aluminum foil, and flash frozen on a dry ice acetone bath. The frozen samples are stored at -70 C and shipped on dry ice to the CRO for bioanalysis.

. All containers and tubes must be labeled. The printed information must include the study number, patient identification number, treatment period, and scheduled sampling day and time. No other information will be written on the labels.

Preparation of Plasma Pharmacokinetic Samples

1. Draw blood into labeled and chilled 3 mL lavender top K2EDTA Vacutainer tube.

2. Mix the blood with the anticoagulant by gently inverting the tube 8-10 times and immediately place on wet ice.

3. Centrifuge the blood samples for 10 minutes at 1006g at 4º C in a refrigerated centrifuge within 10 mins of sample collection

4. Immediately following centrifugation, gently remove the plasma from the packed cells and aliquot into two transfer vial filled with lyophilized citric acid. Each aliquot should contain exactly 0.5 mL of plasma.

5. Vortex split tubes thoroughly. Any remaining plasma post split1/split 2 sample aliquots should be discarded following appropriate biohazard disposal procedures.

   NOTE: If < 0.5 mL plasma is obtained post centrifugation, do not process or store split1 or split2, record split1: ISV (Insufficient Sample Volume), split2: ISV. If < 1.0 mL plasma is obtained post centrifugation, process and store split1 according to procedure; do not process or store split2, record split 2: ISV. Discard remaining plasma using appropriate biohazard waste disposal procedures.

6. Replace cap on tube and freeze the samples immediately at -70°C

Note: No more than 60 minutes should elapse between blood collection and freezing the plasma samples.

7. Keep samples frozen at -70°C or lower until shipment.

Note: Wet ice is defined as a mixture of ice and water

Radius of rotation (rotor arm length) (cm)	**RPM speed needed to achieve 1000g**
4	4743
5	4242
6	3873
7	3585
8	3354
9	3162
10	3000
11	2860
12	2738
13	2631
14	2535
15	2449

Excel formula if rotor length not listed in above table:
RPM = SQRT((1006/(0.00001118*rotor length in cm))

Questions regarding handling the plasma pharmacokinetic specimens should be addressed to the contact person designated by Millennium.

Shipment of Pharmacokinetic Tissue and Blood Samples

All pharmacokinetic samples must be sent to the bioanalytical laboratories specified below in a single shipment at the end of the study or in multiple shipments as agreed upon with the lab (MLN9708 PK samples currently have 618 days of stability and will need to be analyzed before reaching the end of their stability). An inventory list must be included with each shipment. The inventory list must note each specimen drawn for each patient, and note any missing specimens.

The investigator must follow the instructions below:

- For all international shipments, a courier will be designated.

- Notify the bioanalytical laboratories and the designated courier at least 24 hours in

advance of the planned shipment. Provide the designated courier with the appropriate account number to be used, if applicable.

- Samples should be shipped via overnight delivery only on Monday through Wednesday, excluding holidays.
- Double-bag the frozen samples for each patient in bags that can withstand dry ice conditions.
- Pack the frozen samples in sufficient quantity of dry ice in appropriate containers, to maintain a frozen state for at least 3 days.
- Avoid direct contact between sample bags and dry ice by separating them with a dry ice resistant material (eg, newspaper).
- For all biological samples, follow the International Air Transport Association (IATA) regulations for shipment.
- Ensure that the total package weight does not exceed 27.2 kg (60 pounds).
- Label the package with the sponsor-investigator name and study number.
- Include a return address (which includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for the shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment in the study files.

As soon as shipment day and air bill number(s) are available, the site must call or fax the bioanalytical laboratories. The call or fax must specify the study number, number of packages shipped, the number of pharmacokinetic samples, and the time of shipment pick-up.

Ship To:

Covance
115 Silvia Street

West Trenton, NJ 08628, USA
ATTN: Sample Management
Phone # 609-434-0044 X113
christina.lohman@labcorp.com
james.albanese@labcorp.com
batesc1@labcorp.com